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General Policy Issues

The dangers of counterfeit and substandard active pharmaceutical ingredients

WHO was first alerted to the circulation of counterfeit pharmaceuticals at the Conference of Experts on the Rational Use of Drugs held in Nairobi, in 1985. Since then, concern about the situation has been voiced repeatedly by delegations at the World Health Assembly and this has been reflected in several resolutions. The most important was adopted in May 1988 (1) and requested WHO "to initiate programmes for the prevention and detection of the export, import and smuggling of falsely labelled, spurious, counterfeited or substandard pharmaceutical preparations and to cooperate with the Secretary-General of the United Nations in such cases when the provisions of international drug treaties are violated".

The WHO Secretariat has implemented these resolutions through its normative activities as well as in the formulation of guidelines. It has set out to stimulate collaboration between regulatory authorities, and a data base has been created within WHO which contains some 700 case reports on counterfeit finished dosage forms. Information and news are exchanged regularly with other interested parties and drug alerts are circulated to drug regulatory authorities. Particular importance is placed on the promotion of training for drug regulators and inspectors in those countries which are most vulnerable to counterfeiting and related activities.

The report of a WHO/IFPMA workshop held in 1992 (2) defines a counterfeit medicine as one which is deliberately and fraudulently mislabelled with respect to identity and/or source. This definition is also relevant to active pharmaceutical ingredients (APIs) and underscores the need to establish their true origin and to have this information reflected on the label. Furthermore, it has become evident that both developed and developing countries alike are confronted with similar problems. Counterfeits can range from highly sophisticated copies which are almost indistinguishable from the authentic branded product, to potentially dangerous substandard or spurious preparations sold under branded or generic labels.

In countries where there is strong regulation, counterfeits are fewer in number, but highly sophisticated. Where the risk of detection is lower, the infringements increase in number and the misrepresentations become more crude. In the developing countries, it is the essential life-saving drugs such as antibiotics and antiparasitics that are most commonly counterfeited. Many developing countries are heavily reliant on imports of finished dosage forms and active pharmaceutical ingredients. As a result of the attention that has repeatedly been drawn to the extent of counterfeit and substandard products, including APIs, circulating within these countries, the WHO Certification Scheme is being extended to include active pharmaceutical ingredients.

It must be underscored that, at present, the legal status of APIs differs fundamentally from that of finished dosage forms. APIs are not subject to marketing authorization, although they are regulated indirectly through the drug master file (DMF). However, this mechanism is only applied in highly developed countries and, even there, marketing and labelling are not always regulated. Finished dosage forms, on the other hand, are subject to marketing authorization, and their labelling is strictly regulated and requires display of the marketing authorization holder, even when this is not the manufacturer.

Because of the present lack of regulation of APIs, it is unclear whether the definition manufacture and manufacturer— as set out, for example, in the WHO/GMP text (3) and in Directive 75/319/EEC — also covers APIs. If it does, the opportunity arises for a company or an individual involved in "partial manufacture"— perhaps only repackaging — to place their name on the label without further reference to the manufacturer responsible for the chemical synthesis. In many instances, this practice provides a means to deliberately obscure the true provenance and quality of the material.

Case reports
The following reports on counterfeit APIs have been provided to WHO, and several of them clearly illustrate the problem of labelling.
**Australia**

In February 1997, the Therapeutic Goods Administration of Australia drew the attention of the Pharmaceutical Inspection Convention (PIC-PIC/S) Committee of Officials (4) to the practice of substitution. The following cases, concerning APIs manufactured and supplied from Asia, are drawn from the evidence provided.

An API, sulfamethoxazole, manufactured in India and delivered to an Australian firm, was partially substituted with sugar in the same particle size. The substitution involved three of every 10 containers in the delivery. In another incident, inferior grade and rejected APIs were deliberately being placed at the bottom of every third or fourth drum. During subsequent investigations, it came to light that this substitution often takes place immediately following departure of the consignment from the premises of the legitimate manufacturer. Substitution racketeers also gain access to sophisticated packaging technology, including access to “tamper-proof” security devices through co-opting company employees into providing packaging information, or examples of the security, or the actual packaging material from either the manufacturing plant or the printer of the labels.

Information on this particular situation was passed on to all members of the PIC-PIC/S, and inspectors were requested to report any similar problems occurring in their own country. They were also asked whether a provision for “top, middle and bottom” sampling of each container of API received from specified countries should be implemented.

The Therapeutic Goods Administration has also investigated the following cases.

- An antibiotic API exported to Australia from a country in Western Europe was in fact manufactured in Central America, then sent to the European company where it was repackaged, reanalysed and issued with a new certificate of analysis before being shipped to an affiliate in Australia. The label and documentation gave the impression that the API originated in Europe. The Australian company only discovered the origin of the product after an investigation.

- An orphan drug API, documented as originating from a Western European country, was actually produced in Eastern Europe. The practice went undetected by the Australian affiliate company for about a decade until the Western European plant was closed down and information was disclosed. The argument provided by these companies was that the value-added nature of the work conducted in Western Europe was greater than 50% of the cost of the drug provided to Australia and hence the company was entitled to claim that it was “made” in that particular country. No action could be taken since the Australian companies had not committed an offence, and no prosecution of the overseas companies from within Australia was possible. However, because of lack of regulation of either the manufacturing process, *de novo* synthesis, or repackaging, and the routing of subsequent exports, it is unlikely that the authorities in any of the countries involved would have had a basis for legal intervention.

Many similar cases involve substitution, dilution or adulteration, including the addition of subpotent material to normal material in such a way as to be just able to pass pharmacopoeial specifications, and the switching of technical grade for pharmaceutical grade substances.

**United States of America**

Information has also been received from the US Food and Drug Administration’s Office of Criminal Investigation (5) regarding recent cases involving APIs. The following investigation was carried out jointly with the US Customs Service.

In 1991, chemists at SmithKline Beecham Laboratories notified the FDA of the delivery of counterfeit oxytetracycline at their Animal Health Facility in Nebraska. Investigations discovered a conspiracy to import and distribute counterfeit bulk drugs. As a consequence, a company and three individuals were fined for drug counterfeiting and money laundering.

The investigation determined that company employees were switching national drug codes (NDCs) and producing counterfeit certificates of analysis (COAs) reflecting false codes, false manufacturers and false batch-code information. In essence, the legitimate API was replaced with counterfeit API, or repackaged into drums that were different from those used by the legitimate manufacturer. The legitimate drug was therefore replaced with a drug which purported to be the approved US API, when in fact it was not.

Surprisingly, legitimate firms receiving the counterfeit products did not bother to challenge the deliveries, even when they observed unusual or mismatched drums. The drugs involved were chlortetracycline, oxytetracycline, tetracycline,
chloramphenicol, gentamicin, neomycin sulfate, sulfadimidine, and methyldopa.

United Kingdom
Examples of prosecuted cases (6) on which information is provided from the United Kingdom involve pharmaceutical products and not APIs. However, the way in which they were handled could equally apply to APIs and the following examples may be of interest.

• A licensed UK wholesale distributor was found to have stocks of pharmaceutical products on premises other than those declared on the licence. These products were imports for which the company did not have marketing authorization. The products had been removed from original containers and repackaged to disguise the origin, and the expiry dates were extended beyond the shelf-life. As a consequence of this investigation, the operating licence was withdrawn and the company and its owner successfully prosecuted.

• An unlicensed trader was found to import large quantities of pharmaceutical products from outside the European Union, and manufactured on unlicensed sites. These were sold to pharmacies “from the back of a van”. The trader was arrested and the stock seized, as were the proceeds of the sales. Both the trader and an accomplice were successfully prosecuted and pharmacists purchasing the products were reported to their professional association.

• A licensed wholesaler who substituted batch numbers on a substantial quantity of stock he was not licensed to sell was successfully prosecuted.

Cases still under investigation in the UK involve illicit manufacture, obtaining APIs from unlicensed sites in the Far East, assembling products and proposing these as the genuine product, and assembling products containing only 50% of the API.

A counterfeit product in the UK tends to be a prescription-only medicine and one for which either demand and sale price are high, or for which there is a specialized highly-priced demand.

Prosecutions generally result in fines and, occasionally, a prison sentence. United Kingdom legislation permits sequestration of assets gained by unlawful activity, and the Medicines Control Agency can request courts to confiscate property, money and other assets. Consignments of pharmaceutical products are also seized. These actions are intended to make counterfeiting activities unrewarding and, as a deterrent, can be more effective than fines or even imprisonment.

Contamination with diethylene glycol
Experience with this compound indicates that safeguards need to be applied to all materials included in formulated dosage forms and not just APIs. Contamination or substitution with diethylene glycol in the manufacture of pharmaceutical products has resulted in the loss of over 500 lives — mostly children — in Argentina, Bangladesh, India, Nigeria and, now, Haiti. WHO has sent warnings to drug regulatory authorities in all Member States following these incidents.

Over 80 children died in the Haiti incident last year (7), and the case was investigated by the Haitian authorities with the assistance of the US Food and Drug Administration (FDA), the US Centers for Disease Control (CDC) and WHO/PAHO. A special workshop on diethylene glycol contamination was subsequently held and a report will soon be issued with recommendations on this particular problem. It will also include simple analytical test procedures that allow the detection of diethylene glycol down to a low content limit.

Despite the fact that the pharmaceutical company in Haiti ordered glycerol from a company in Germany, the material was originally shipped from Xiangang (China) via the free port in Rotterdam (Netherlands) to Port-au-Prince. It is clear that throughout a series of complicated and numerous transactions, vital information on the provenance and nature of the material was obliterated on documents and product containers.

The pharmaceutical company in Haiti used the product traded in this way for the preparation of paracetamol syrup and oral drops for neonates. Following the incident, the manufacturer was visited by an FDA inspector and found to be in violation of basic GMP principles, since the incoming starting materials were not being tested, no in-process quality control was implemented, and certificates of analysis were not always available. According to a newspaper article on this case, the manufacturer stated that he had ordered the material from Germany to be certain of its quality.

What can be done?
There is now sufficient evidence of the international circulation of counterfeit and substandard APIs and other starting materials used in the manufacture of medicines. The magnitude of this trade may be unknown, but it is certainly far greater than is evident from the case histories that have filtered through into the public domain. The range and extent of illicit activities, even in highly regulated countries, points to an urgent need for countermeasures which should be coordinated on a global basis. The following recommendations may provide ways to consolidate efforts against unlawful and dangerous activities.

**Drug regulatory authorities should:**
- extend their regulatory mandate to cover manufacturers of APIs — particularly with regard to inspection of GMP compliance, and impose rigorous requirements for labelling and certificates of analysis for consignments moving in international commerce.
- introduce regulations that require APIs and all other starting materials intended for the formulation of medicinal products to be clearly labelled "for pharmaceutical use" or with a suitable pictogram.
- establish within the regulatory authority a multidisciplinary group to investigate illicit activities promptly and professionally.
- monitor free ports and strengthen collaboration with law enforcement agencies including customs officials, and offices of criminal investigation, at national and international level.
- seek to enact legislation that permits sequestration of assets gained by unlawful activity and seizure and destruction of products involved.

**WHO should:**
- develop a network of technically competent officials within national drug regulatory authorities with a view to ensuring timely exchange of information, both on cases of counterfeiting and on any countermeasures taken at national level.
- act as a clearinghouse for the exchange of information on counterfeit pharmaceuticals and APIs.
- develop guidelines for the certification of APIs moving in international commerce and strengthen GMP.
- continue to promote the use of WHO guidelines on GMP, inspection and drug registration.

**Pharmaceutical manufacturers, wholesalers and traders should:**
- be cautious in the procurement of APIs and finished products, and when introducing products into the distribution chain.
- maintain vigilance in detecting counterfeiting or substitution of dosage forms and APIs.
- share information with regulatory authorities. This information should be handled with due discretion to avoid loss of confidence in legitimate products.
- rigorously implement GMP in the manufacture of APIs (3).

**Manufacturers of finished dosage forms should:**
- buy APIs, whenever possible, from the original manufacturer or, when through traders, insist on transparent and full documentation concerning the origin, and demand certificates of analysis.
- be aware of their responsibility and liability in assessing and ensuring the quality of the APIs and other starting materials that they use, and the rigorous conditions, as outlined in GMP (3), to be applied in those exceptional situations where reliance is vested in the supplier’s certificate of analysis in place of a full re-analysis.

Interested parties must decide to what extent these recommendations are realistic. The impact of additional laws and regulations will depend on their implementation, and this will require increased inspection capacity and more resources. The full responsibility of the manufacturer cannot be overstressed and the supplier must inform the manufacturer of the true origin of the API. Many small manufacturers in developing countries may have little bargaining power to insist on this transparency, and action needs to be considered with urgency to protect all concerned.

**References**
1. World Health Assembly resolution WHA 41.16.
3. WHO Expert Committee on Specifications for Pharma-


Quality Assurance Issues

The importance of analytical procedures in regulatory control

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A regulatory authority responsible for the quality of the pharmaceutical products distributed within its jurisdiction is confronted with many challenges in its efforts to assure the public health of its citizens. One of the primary tasks of regulation is to determine which products can safely be allowed onto the market. This is usually accomplished through a drug registration system.

The laboratory resources needed to support the regulation of any given market will depend heavily on whether or not the products are manufactured within that market area or whether they are largely imported. Consequently, if the market is important and handles large quantities of products, the official laboratory will need sufficient resources to provide an analytical service which will assure the quality of these products. This is especially important when products proposed for entry into the area have been manufactured in facilities which have not had direct inspection for compliance with good manufacturing practice (GMP).

In many developing countries, however, an unfortunate combination of two factors exists. On the one hand, there is a predominance of imported finished products and on the other, a lack of adequate analytical services. Product quality can be better assured if an inspection force is available to periodically visit manufacturing sites and review production records. Although the United States market is supplied mainly by manufacturers operating within its borders, the number of finished dosage forms entering the country is steadily increasing. It is furthermore expected that the current globalization of the pharmaceutical market will also give impetus to increased trading in finished dosage forms and this situation will demand even greater efforts by inspection and laboratory services.

Once drug registration has been established, compliance of the approved products with quality standards must be sought. In some instances, where a country depends largely on imported finished products, a regulatory authority will apply the same methods of analysis and quality standards as those in the country of product origin. Since little harmonization has so far taken place among the major pharmacopoeias, this could give rise to a situation where several different quality standards and methods of analysis are in use for the same product within a given country or market area.

The multiplicity of standards and methods applicable to the same product can result in an extremely complicated situation for the regulatory control services, such as the need to have access to each pharmacopoeia and the specific equipment and reagents used in the country of origin. In an effort to remedy this situation, it has been suggested that the establishment of a unique analytical monograph for registration purposes and an accompanying quality standard for each finished dosage form would help to ensure that the approved product conforms to the same standards. However, this undertaking would constitute an immense task, and an easier solution may be the adoption of specific monographs and quality standards for each approved product based on existing pharmacopoeias.

When a pharmaceutical product is received at a port of entry, it is subject to controls to determine its marketing status, labelling, and claimed ingredients. These determinations should be made on all products entering the market area. In order not to hold up shipments, analytical tests to substantiate the claimed product characteristics are needed rapidly and as near to the port of entry as possible. However, this is not always possible, since a market area can very often be serviced by multiple ports of entry and standard laboratory services are not necessarily available at all of them. In this situation, a preliminary screening can be made of the product to ascertain the presence of the active ingredient and the claimed amount. In order to be effective, this analysis must be carried out before
release of the goods. If this is not the case, the products will be distributed throughout the country and regulatory controls would be ineffective in the event that a product needs to be withdrawn. An array of chemical methods of analysis are available to provide information on the quality of a product and ensure that it complies with the regulatory requirements in force. This availability is, however, dependent on many factors such as funding and the extent to which these services are required. Consideration must additionally be addressed to sources of funding for staff, training, equipment, maintenance, supplies and running costs.

A preliminary screening at a port of entry will provide information on whether a product is approved for distribution, is properly labelled, contains the correct ingredient in the claimed amount and complies with legal specifications. It is at this point that counterfeit products can most conveniently be identified. Screening techniques include WHO basic tests, and other simple test methods. However, the use of thin layer chromatography (TLC) has been shown to be particularly useful during this preliminary screening phase. The tests are cheap and quick, require a low capital investment and have low operating costs. TLC requires minimum laboratory resources and analyst skills, which means that competent personnel can be easily trained in their use. Any sample found to fail the necessary tests using this method could then be subjected to analysis according to the legal reference methods (LRM) carried out by the regulatory control laboratory. Notwithstanding the simplicity of the method, TLC is reliable enough to support decisions on whether entry should be denied for products which fail significantly.

Once a product has entered the market and has been distributed, it falls within the jurisdiction of that market. This generally means that any regulatory action taken against the product must be based on LRM as determined by legislation. Thus, in addition to providing preliminary screening of imported products, regulatory authorities must maintain, or have access to, facilities suitable for conducting LRM which will confirm or refute the preliminary screening results. These facilities are also useful for carrying out special surveillance activities. Preliminary screening, with possible confirmatory LRM activities, is therefore essential before a product can be released into the market area, and to ensure that the product will comply with the claimed expiry date and required quality standards. Unfortunately, in the case of the LRM, several days or weeks may be needed to set up the analytical equipment and prepare the reagents. In addition, many LRM use liquid chromatography (LC) or gas-liquid chromatography (GLC) methods. The United States Pharmacopeia, for example, contains over 800 monographs requiring LC and 150 monographs requiring GLC. As can be imagined, equipment for this type of analysis requires a relatively large capital investment, with the related costs for trained operators and maintenance staff. In the United States, a high-performance liquid chromatograph will cost approximately $25 000 to $65 000 depending on the accessories and attachments, and a gas-liquid chromatograph will cost between $15 000 and $70 000, although less expensive equipment may be available in other regions of the world. In order to keep the equipment operational and to replace worn parts, a laboratory will need an additional 5–10% of the initial cost for maintenance. It is important to have easy access to parts and circuit boards in addition to the necessary reagents, reference standards and supplies, the cost of which may represent a further 5–10% of the initial outlay. Furthermore, operation of the equipment can be affected by environmental factors such as temperature and humidity.

Experience with running an LRM facility suggests that, in order to be efficient, it should be equipped and staffed at a level over and above minimum requirements and it is often preferable to have three or more units of identical equipment so that aberrant results can be confirmed by a second apparatus. Also, modules can be switched around or exchanged when defective parts are identified. Multiple units of identical apparatus will also reduce the need for space to house spare parts and consumable supplies required to keep the equipment operational.

The acquisition of expertise is also an important factor if the laboratory is to be run successfully. In contrast to the minimum skills needed for applying the preliminary testing methods, personnel carrying out LRM need higher levels of training. In the more complex laboratory environments, it is useful to have several persons skilled in the same techniques working together in order to stimulate the functioning of the laboratory and discuss details of the work. This strengthens the analytical capability of the services provided and assists in the application of the more complicated instrumental techniques.
Because of the costs involved, LRM testing can only be performed on a fraction of the products actually in circulation and in many cases this is below 1% of the total. For example, in a country where 35,000 prescription-only medicines and 115,000 over-the-counter products are on the market, there would be 150,000 batch samples to be collected and analysed. For each product, analysis would include assay, content uniformity, release rate and identity and an approximate total of 30 analytical results would eventually be produced taking approximately one week per sample to complete. For the sake of statistics, it may be worth while for a regulatory authority to collaborate with industry in estimating the number of batches manufactured annually within the territory in order to compare these figures with the number of batches tested for compliance.

In some special cases, a product may need further testing using advanced analytical methods. For example, in the case of an epidemiological aberration associated with a specific product or in detection of counterfeit or spurious products. These methods will also provide a means of verification of the techniques proposed by manufacturers in the registration dossiers and may assist in carrying out research into detecting unexpected impurities, undeclared or substituted excipients or other characteristics which need examination. In this case, mass spectrometric, nuclear magnetic resonance, or X-ray powder diffraction analysis may be required. This can only be carried out by skilled staff backed by an armamentarium of sophisticated equipment normally available only at universities and research institutes. Access to this expertise should be facilitated whenever possible by the authorities.

It is therefore important that the regulation of pharmaceutical products in every country should include responsibility for the quality of products circulating within its boundaries and those entering the market area from other parts of the world. This can only be achieved through a three-tiered system of preliminary and legally required methods (LRM) backed up by advanced analytical methods. This will enable large numbers of products to be screened to ensure identity and content amount, with an LRM level to validate the results of these techniques, confirm marginal findings and determine conformity with legal requirements. Advanced analytical methods will be relied on when sophisticated counterfeit products need to be identified or to confirm or refute circumstances of product-related, epidemiological events.

Further reading


Reports on Individual Drugs

Simplified treatment for leprosy

Leprosy is caused by a bacillus, *Mycobacterium leprae*, which multiplies very slowly in the body and affects the skin, nerves and mucous membranes. In many cases, symptoms do not become visible for many years. If left untreated, the disease can cause progressive and permanent damage to skin, nerves, limbs and eyes.

The WHO Action Programme for the Elimination of Leprosy has been set up to actively seek resources and assist in elimination activities in the 55 countries which have been identified as endemic. Of these, only 16 are rated as "most endemic", but they account for 91% of all cases. Provided that these countries are able to maintain and intensify case-finding and treatment, and that resources continue to be available, WHO is confident that leprosy will soon be eliminated as a public health problem.

Multidrug therapy (MDT) has been used against leprosy since 1981, and is a combination of three powerful drugs — dapsone 100 mg daily, rifampicin 600 mg once monthly, and clofazimine 300 mg once monthly and 50 mg daily. This treatment regimen will effectively kill the bacteria and prevent drug resistance. The drugs are highly acceptable to patients, causing very few side-effects and there is virtually no relapse. Because the treatment has proven to be so effective, a WHO Expert Committee has now agreed that the course of treatment for multibacillary leprosy may be shortened to 12 months rather than the current 24 months.

With the early detection and increasing coverage of patients by MDT, the cases diagnosed each year are increasingly milder and, currently, multibacillary leprosy constitutes a very small proportion of the total disease burden. Newly detected skin-smear positive cases have fallen sharply from close to one million ten years ago to an estimated 70 000 worldwide in 1996.

In patients with paucibacillary (PB) leprosy, having few bacteria in the body and only one skin lesion, it is now considered sufficient to use a single dose of three antileprosy drugs. A recent multicentre trial has shown that one dose of rifampicin 600 mg, ofloxacin 400 mg and minocycline 100 mg is sufficient to cure patients with PB leprosy exhibiting a single skin lesion, and provides an acceptable and cost-effective alternative regimen. For PB leprosy patients with more than one skin lesion, the standard treatment of rifampicin 600 mg once monthly and dapsone 100 mg daily for a duration of six months is still recommended. WHO is currently providing these drugs in blister packs, free of charge and in sufficient quantities to treat about 800 000 patients per year. This treatment has successfully been used to cure 8.4 million sufferers of all forms of the disease since 1981.

Unfortunately, for many years to come, countries will still be confronted with the problem of rehabilitation for those people who suffered severe damage to limbs or eyes through lack of treatment in the past. However, provided the political will and the resources needed for treatment are maintained, it is reasonable to envisage the total eradication of leprosy as a disease in the not so distant future.


Should antibiotics be indicated for children with acute otitis media?

Acute upper respiratory infections (URI) that affect the ear, nose and throat are common worldwide, particularly among children under 5 years of age. Although they are seldom life-threatening in developed countries, this is not always the case elsewhere (1). In disability-adjusted life years (DALYs), otitis media is estimated to cause a burden of over 50 million DALYs, and over 90% of this disease burden falls on developing countries (2, 3).

Chronic otitis media is a serious problem because it can retard language development and the educational progress of children. It therefore requires proper detection and consistent follow-up of affected children (4). Acute otitis media is normally a bacterial or viral infection of the middle ear, and is usually secondary to URI or a complication of...
measles or pertussis. In children, the incidence peaks between 6 and 15 months. By the age of 3 months, 10% will have suffered at least one episode (5).

The use of antibiotics for acute otitis media in children varies between countries — from as low as 31% in the Netherlands to as high as 98% in Australia, the United Kingdom and the United States (6). A meta analysis of randomized, controlled trials has now been completed to determine the usefulness and effect of antibiotic treatment in acute otitis media in children (7).

Six studies in children aged between 7 months and 15 years with acute otitis media were evaluated. Pain, deafness and other symptoms related to acute otitis media were used as main outcome measures. The evaluation showed that as many as 60% of placebo-treated children were pain-free within 24 hours of presentation and at 2–7 days after presentation, antibiotics reduced pain in the remaining children. Early antibiotic use (most commonly penicillin or amoxicillin) reduced pain by 41%. Antibiotics also reduced contralateral acute otitis media by 43%, but seemed to have no influence on subsequent attacks of acute otitis media or deafness at one month, although there was a trend for improvement of deafness at three months. On the other hand, antibiotics were associated with a near doubling of the risk of vomiting, diarrhoea or rashes.

Only one study (8) has investigated the possible consequences of not using antibiotics. For a period of 17 months, 60 general practitioners in the Netherlands had used nose drops and analgesics alone for initial treatment of acute otitis media in 4860 children aged between 2 and 12 years of age. Only 126 (2.7%) of these children suffered a severe course of illness, which was measured by third or fourth-day illness, or ear discharge for more than 14 days. One hundred of these patients with severe symptoms entered the trial treatment schedule, which showed antimicrobial treatment, either alone or in combination, to be more effective than myringotomy alone. Two of the children developed mastoiditis, but this settled uneventfully after treatment with amoxicillin.

This study indicated that acute otitis media in children can be treated with nose drops and analgesics alone for the first three to four days but if this is not effective, antibiotics should then be administered. From the above studies, it can be concluded that early use of antibiotics provides only modest benefit for acute otitis media. None the less, it must be pointed out that studies have so far only been conducted in developed countries. The results may therefore not be generally indicative of the situation in developing countries where a far greater risk of serious complicated suppuration may support the routine early use of antibiotics (1). Perhaps the best approach is still to regard antibiotics as an optional treatment for early acute otitis media and, where possible, physicians should discuss with the patients and their parents the risks and benefits associated with this and other optional treatment.

References

Acetylsalicylic acid: confirmed efficacy after stroke

Stroke and other cerebrovascular diseases kill about 4 million people a year, and this figure represents 7.5% of total global deaths from all causes (1). Stroke is also a major cause of handicap in middle-aged and elderly people, and attacks can cause partial paralysis or impairment of speech and other mental faculties. The care of these patients thus poses a growing problem for health services in both developed and developing countries.
Stroke is caused by acute occlusion of a cerebral artery. Anticoagulants have been widely used (2–4) to facilitate early clot lysis, to inhibit clot propagation in cerebral arteries and to prevent early arterial re-embolization and venous thromboembolism originating in immobile limbs (5).

Acetylsalicylic acid (ASA) has been shown to be effective in the treatment of acute myocardial infarction (6). Moreover, long-term antiplatelet therapy among patients with a history of myocardial infarction, stroke or transient ischaemic attack has shown that about 40 similar types of serious vascular events are avoided per 1000 patients if treatment with ASA was begun some years previously. However, until now, only limited clinical trials have compared antithrombotic therapy groups versus control groups in acute ischaemic stroke and none has been large enough to provide reliable evidence on the safety and effectiveness of early ASA for acute ischaemic stroke.

Two large multicentre trials, which have been set up to investigate the usefulness of antithrombotic therapy in acute ischaemic stroke, have now reported their findings. The International Stroke Trial (IST) (7) was a randomized, open trial of acetylsalicylic acid, subcutaneous heparin, both, or neither, among some 20 000 patients from 467 hospitals in 36 countries. The Chinese Acute Stroke Trial (CAST) (8) was a randomized placebo-controlled trial of early ASA use (160 mg/day) in 20 000 patients with acute ischaemic stroke in 413 Chinese hospitals. Both trials applied computed tomographic (CT) scanning to confirm the diagnosis of ischaemic stroke. In the IST, 67% had a CT scan before randomization, a further 29% were scanned after randomization, and 4% never had a CT scan. In the CAST, 87% had had a CT scan before randomization, and 94% had at least one CT scan in hospital.

In the IST, neither of the heparin regimens (5000 IU or 12 500 IU twice daily) offered any clinical advantage at 6 months. For ASA taken at 300 mg daily the IST showed a small but worthwhile improvement at 6 months. There was already a significant reduction of 11 (SD 5) deaths or non-fatal recurrent strokes within 14 days per 1000 patients. In CAST, there was a significant 14% (SD 7) promotional reduction in mortality during the scheduled treatment period of 343 deaths (3.3%) among ASA-allocated patients versus 398 deaths (3.9%) among placebo-allocated patients.

There were significantly fewer recurrent ischaemic strokes in the ASA-allocated, rather than in the placebo-allocated group (167 and 1.6% versus 215 and 2.1%), but slightly more haemorrhagic strokes.

These results match those of the small MAST-I study, which is the only previously published study on ASA in acute stroke. The authors of the CAST study analysed all three trials: MAST-I, CAST and IST. In CAST, there were 11 (SD 6) fewer patients either deceased or dependent at discharge per 1000 allocated ASA; in IST, with assessed disability at 6 months, there was a similar benefit of 13 per 1000. For these two trials, together with MAST-I, the benefit is 13 (SD 5) fewer dead or dependent per 1000. This finding also provides substantial reassurance that the early use of ASA does not increase the prevalence of serious disability among survivors.

The results of IST provide evidence against the routine use of heparin as an intensive or subcutaneous medium-dose regimen in patients with acute ischaemic stroke. The hypothesis that ASA plus low-dose heparin is better than ASA alone remains unresolved by this trial given the relatively small number of patients, since it was concluded that a trial of at least 20 000 patients would be required. Because the evidence from ASA trials involved some 40 000 randomized patients, it is more reliable than the conclusions which could be drawn for use of heparin.

Unless there are clear contraindications, immediate use of ASA in an initial dose of 300 mg —though a lower maintenance dose might suffice — should be considered in all patients with acute ischaemic stroke, especially if a CT scan has excluded intracerebral haemorrhage. Long-term low-dose ASA, continued for some years after the stroke, will improve the prognosis for many patients and IST and CAST showed a slight improvement in prognosis if ASA is started at the beginning rather than at the end of the hospital stay.

The results of these large clinical trials and the treatment recommendations made by the authors have been reviewed extensively (9–11), and more investigations may be needed to draw conclusions on the value of heparin and other thrombolytic therapies, such as alteplase (1). None the less, CAST and IST are particularly relevant since the trials were conducted in a wide variety of specialist and non-specialist hospitals in 37 different countries throughout the world.
Acetylsalicylic acid treatment can be used advantageously in countries where there are limited medical resources since laboratory monitoring is not necessary. It is also important to note that for about 800 of the 40 000 patients in CAST and IST, the initial diagnosis was wrong and these patients had cerebral haemorrhage. However, there was no indication in either trial that these misdiagnosed patients were somehow damaged by ASA and, if there were any side effects at all, they were not significant enough to report.

References

Antiretroviral therapy for HIV: latest guidelines

The United States Department of Health and Human Services (DHHS) has recently published guidelines on the use of antiretroviral agents in HIV-infected adults and adolescents and laboratory monitoring methods in the treatment of HIV-infected individuals (1). These have been developed by an expert panel brought together by the DHHS and the Henry J. Kaiser Family Foundation. The guidelines are directed to physicians and other health care providers and are intended as a companion document to the therapeutic principles formulated by the National Institutes of Health (NIH) Panel (2).

The guidelines address the following issues:

• testing for plasma HIV RNA levels (viral load) and CD4+ T lymphocyte count;
• when to initiate therapy in established HIV infection;
• therapy in patients with advanced stage disease;
• interruption of therapy;
• changing therapy and available therapeutic options;
• treatment of acute HIV infection; and
• antiretroviral therapy in pregnancy.

These guidelines differ in many respects from those issued in April 1997 by the British HIV Association and published in the previous issue of this journal (3, 4). This reflects the evolution of current therapy and the urgency with which information from ongoing clinical trials is communicated to health care professionals. Practitioners caring for HIV-infected persons must keep abreast of these developments in order to offer the latest advice on the safe and effective use of the new therapies.

The following is a selected summary of the main recommendations from the guidelines.

Testing for HIV

Decisions regarding initiation or changes in antiretroviral therapy should be guided by monitoring of the laboratory parameters of viral load (plasma HIV RNA), the CD4+ T lymphocyte count and the clinical condition of the patient. Confirmatory laboratory tests should be performed whenever possible.
In previously untreated patients, viral load (plasma HIV RNA levels) and CD4+ T lymphocyte counts should be measured at the time of diagnosis and generally every 3–4 months thereafter. Viral load should also be measured immediately prior to and 4 weeks after initiation of antiretroviral therapy. This allows the clinician to evaluate the initial effectiveness of therapy. The absence of a large decrease (less than 10-fold) in viral load by 4 weeks should prompt the physician to reassess patient adherence, rule out malabsorption, consider repeat RNA testing to document lack of response, and consider a change in drug regimen. With optimal therapy and using currently available assays, viral levels in plasma should be undetectable at 6 months from start of treatment.

A minimally significant change in plasma viraemia is considered to be a 3-fold increase or decrease, and in CD4+ T lymphocyte count, a drop of more than 30% from baseline for absolute cell numbers and a drop of more than 3% from baseline in percentages of cells.

**Therapy in asymptomatic HIV**

Antiretroviral therapy provides clinical benefit in HIV-infected individuals with advanced HIV disease and immunosuppression. Although there is a theoretical benefit in treating patients with a CD4+ T cell count greater than 500 cells/mm³, no long-term clinical benefit has yet been demonstrated.

Factors outweighing initiation of early treatment in the asymptomatic stable patient include potential adverse effects of the drugs on the quality of life, a risk of drug resistance limiting future treatment options, the risk of dissemination of virus resistant to protease inhibitors and other agents, the unknown durability of effect of currently available therapies, and the unknown long-term toxicity of some drugs. The guideline lists several factors to be considered, including the willingness of the individual, after counselling and education, to adhere to a complicated prescribed therapy and to accept the side-effects of treatment.

Once the patient and physician have decided to initiate therapy, this should preferably be aggressive, with the intention of suppressing the plasma viral load to undetectable levels. In general, any patient with fewer than 500 CD4+ T cells/mm³ or more than 10 000 (bDNA) or 20 000 (RT-PCR) copies of HIV RNA per ml of plasma should be offered therapy.

The preferred regimen in established HIV infection is two nucleoside analogues (NRTIs) and one potent protease inhibitor selected from the following columns where drugs are listed in random, not priority, order:

<table>
<thead>
<tr>
<th>Protease inhibitors</th>
<th>Nucleoside analogues</th>
</tr>
</thead>
<tbody>
<tr>
<td>indinavir</td>
<td>ZDV (zidovudine) + ddI (didanosine)</td>
</tr>
<tr>
<td>nelfinavir</td>
<td>d4T (stavudine) + ddI</td>
</tr>
<tr>
<td>ritonavir</td>
<td>ZDV + ddC (zalcitabine)</td>
</tr>
<tr>
<td></td>
<td>ZDV+ lamivudine (3TC )</td>
</tr>
<tr>
<td></td>
<td>d4T+ 3TC</td>
</tr>
</tbody>
</table>

**Therapy in advanced HIV infection**

All patients with advanced HIV infection should be treated with antiretroviral therapy, as should all patients with symptomatic HIV infection defined as the presence of thrush or unexplained fever, but without progression to AIDS.

Once therapy is initiated, a maximum suppressive regimen, such as two nucleoside analogues and one protease inhibitor should be used as set out above. Advanced-stage patients maintained on an antiretroviral regimen should not have therapy discontinued during an acute opportunistic infection or malignancy unless there are concerns regarding drug toxicity, intolerance, or drug interactions. Patients who have progressed to AIDS are often treated with complicated combinations of drugs and the potential for multidrug interactions must be carefully considered. The table on page 136 lists some of the known major potential interactions.

In this regard, the use of rifampicin to treat active tuberculosis is problematic in a patient receiving a protease inhibitor, which adversely affects the metabolism of rifampicin. However, this treatment is frequently needed to effectively suppress viral replication in patients with advanced disease. Conversely, rifampicin lowers the blood level of protease inhibitors which may result in suboptimal therapy. While rifampicin is contraindicated with protease inhibitors, one might consider using rifabutin at a reduced dose.

Other factors complicating advanced-stage infection are wasting and anorexia, which may prevent patients from adhering to the dietary requirements for efficient absorption of certain protease inhibitors. Bone-marrow suppression associated with zidovudine and neuropathic effects of zalcitabine, stavudine and didanosine may combine with the direct effects of HIV to render the
## Known potential interactions of protease inhibitors*

**indinavir**
- inhibits cytochrome P450
- not recommended for concurrent use: rifampicin, terfenadine, astemizole, cisapride, razolam, midazolam, ergot alkaloids
- indinavir levels increased by ketoconazole
- indinavir levels reduced by rifampicin, rifabutin
- didanosine reduces indinavir absorption unless taken > 2 hours apart.

**ritonavir**
- inhibits cytochrome P450 (potent inhibitor)
- ritonavir increases levels of multiple drugs that are not recommended for concurrent use
- reduced ritonavir absorption with didanosine unless taken > 2 hours apart
- ritonavir decreases levels of ethinylestradiol, theophylline, clarithromycin, sulfamethoxazole and zidovudine.

**saquinavir**
- inhibits cytochrome P450
- saquinavir levels increased by ritonavir, ketoconazole, grapefruit juice
- saquinavir levels reduced by rifampicin, rifabutin and phenobarbital, phenytoin, dexamethasone and carbamazepine
- not recommended for concurrent use with terfenadine, astemizole, cisapride, ergot alkaloids.

**nelfinavir**
- inhibits cytochrome P450
- nelfinavir levels reduced by rifampicin, rifabutin
- not recommended for concurrent use with rifampicin, triazolam, midazolam, ergot alkaloids, terfenadine, astemizole, cisapride
- nelfinavir decreases levels of ethinylestradiol and norethindrone and increases ketoconazole level.

## Known adverse effects of protease inhibitors*

**indinavir**
- nephrolithiasis — gastrointestinal intolerance
- increased indirect bilirubinaemia (inconsequential)
- headache, asthenia, blurred vision, dizziness, rash, metallic taste, thrombocytopenia
- new or exacerbated diabetes mellitus, hyperglycaemia

**ritonavir**
- gastrointestinal intolerance, nausea, vomiting, diarrhoea
- paraesthesia (circumoral and extremities
- asthenia
- taste perversion
- triglycerides increase > 200%, transaminase elevation, elevated CPK and uric acid
- new or exacerbated diabetes mellitus, hyperglycaemia

**saquinavir**
- gastrointestinal intolerance, nausea, diarrhoea
- headache
- elevated transaminase enzymes
- new or exacerbated diabetes mellitus, hyperglycaemia

**nelfinavir**
- diarrhoea
- new or exacerbated diabetes mellitus, hyperglycaemia

* Taken from Department of Health and Human Services. Guidelines for the use of antiretroviral agents in HIV-infected adults and adolescents Table IX (draft document). See reference 1.

1 FDA Talk Paper, T7–23 1997 (see page 141).
drugs intolerable. Hepatotoxicity associated with certain protease inhibitors may limit their use, especially in underlying liver dysfunction. The absorption and half-life of certain drugs may be altered by antiretroviral agents. Some interactions can result in life-threatening drug toxicity.

Health care providers should inform their patients of the need to discuss any new therapy, including the need to consider the effects of over-the-counter medicines and alternative medications. Careful attention should be given to the relative risks of specific combinations of agents.

** Interruption of antiretroviral therapy **

There are multiple reasons for temporary discontinuation of antiretroviral therapy, including intolerable side-effects, drug interactions, first trimester pregnancy and unavailability of the drug. There are no reliable studies or estimates of the number of days, weeks or months that constitute a clinically important interruption of one or more components of a therapeutic regimen that would increase the likelihood of drug resistance. If there is a need to discontinue antiretroviral medication for an extended time, clinicians and patients should be advised of the theoretical advantage of stopping all antiretroviral agents simultaneously, rather than continuing one or two agents, to minimize the emergence of resistant viral strains.

** Changing a failing regimen **

When considering a change in therapy, it is important to distinguish between drug failure and drug toxicity. In the latter case, it is appropriate to substitute one or more alternative drugs of the same potency and from the same class of agents as that suspected of causing toxicity. Optimally, and whenever possible, the regimen should be changed entirely to drugs that have not previously been taken.

With combination therapy, at least two, and preferably three, new agents must be used. This is based on current understanding of strategies to prevent drug resistance. Special criteria that may prompt consideration for changing therapy include the following:

- less than 10-fold reduction in the plasma viral load by week 4 following initiation of therapy;
- failure to suppress plasma viral load to undetectable levels within 4–6 months of initiating therapy;
- repeated detection of virus in plasma after initial suppression to undetectable levels;
- any reproducible significant increase, defined as 3-fold or greater, of plasma viral load not attributable to intercurrent infection, vaccination or the test method;
- persistent declining CD4+ cell numbers; and
- clinical deterioration.

** Other important aspects **

The guidelines also discuss the treatment of acute HIV infection, treatment regimens for primary HIV infection, patient follow-up, duration of therapy for primary HIV infection and antiretroviral therapy in the HIV-infected pregnant woman including treatment of HIV-infected children.

The panel responsible for drafting the guidelines has reiterated its commitment to revising recommendations as new data become available.

** References **


General Information

Biological standardization: report of the Expert Committee

The WHO Expert Committee on Biological Standardization recommends procedures for assuring the quality, safety and efficacy of biological medicinal products. It also reviews and discusses issues related to the standardization and control of biologicals and establishes international reference materials. Requirements and guidelines are also developed for the production and control of biologicals including vaccines, plasma products and diagnostic agents.

The rapid expansion and increasing diversity of the biologicals sector, together with the development of novel biotechnological methods, raise new and very specific challenges for product safety and efficacy, and call for the establishment and implementation of effective control measures. In this respect, a review of the scientific basis of the standardization and quality control of biologicals has recently been conducted on behalf of the National Biological Standards Board of the United Kingdom. The review was undertaken in collaboration with WHO and with support from the European Medicines Evaluation Agency and the European Pharmacopoeia. Because the report has important implications at international level, the Committee has recommended its issue by WHO to assure maximum dissemination (1).

At the latest meeting of the Expert Committee in October 1996, important changes in recommendations regarding residual DNA in biological products derived from continuous cell lines were agreed and a relaxation was allowed on the extent of chromosomal recharacterization required for well-established diploid cell-lines used in production and tumorigenicity testing. The report of the meeting, which will be published soon in the WHO Technical Report Series, will cover the following issues in detail.

The use of International Reference Materials established by WHO for designating the activity or identity of biological preparations used in prophylaxis, therapy or diagnosis ensures comparability of substance activity, as well as reliability of diagnostic procedures. Their extensive use attests the key role that these materials play in harmonizing the quality of biologicals at international level. The eight new or replacement standards established in 1996 by the Committee are set out in the table on page 139. Additionally, six International Reference Materials have been discontinued, a number of these being antibiotics where the microbiological assay has now been replaced by a physicochemical assay method.

With regard to the supply of International Reference Materials, a decision has been taken by the Statens Seruminstitut, Copenhagen, to relinquish responsibility for this service to the National Institute for Biological Standards and Control (NIBSC) in the United Kingdom. Stocks of reference materials have now been transferred to the NIBSC, and conditions of distribution will be the same as for other International Reference Materials already provided. Tribute was paid to the long and valuable contribution by the Statens Seruminstitut to WHO activities.

Twelve interim Reference Reagents were also established by the Committee (see page 139). This constitutes a new class of reference materials which have been developed — albeit on limited data — to provide rapidly expanding areas, such as cytokine production, with a means for standardization in measurement prior to the establishment of an International Standard. The availability of these Reference Reagents was considered vital for use during the transitional period between laboratory and clinical work.

Three new documents were adopted at the meeting. Revised requirements for cell substrates to be used for the production of biologicals cover use of animal cells as in vitro substrates for the production of biologicals, and incorporate the latest available data relating to cell substrates. They have been adopted following worldwide consultation and discussion at the International symposium on the safety of biological products prepared from mammalian cell culture, held in Annecy, France, in September 1996. The requirements cover the characterization and testing of continuous cell lines and diploid cell lines for the production of both viral vaccines and other biologicals, such as monoclonal antibodies and recombinant DNA products, as well
as some general manufacturing requirements which apply also to primary cells. Considerable emphasis is placed on testing for extraneous agents and manufacturers are clearly encouraged, wherever possible, to use cell substrates for production generated from cell banks which have been thoroughly characterized, rather than from primary cells. In the revised requirements for diploid cell lines the extent of chromosomal recharacterization needed for well established diploid cell lines, such as MRC-5 and WI-38, as well as the extent of routine tumorigenicity testing has been relaxed. There is also a major departure from previous requirements published by WHO concerning the amount of residual cellular DNA permitted in products derived from continuous cell lines. In 1986, a WHO Study Group advised on the levels of

### International Biological Standards and Reference Reagents established by the 46th WHO Expert Committee on Biological Standardization, 1996

**Antibodies**
- Anti-rubella immunoglobulin, human
  - First International Standard

**Blood Products**
- Blood Coagulation Factors IX concentrate, human
  - Third International Standard
- Blood Coagulation Factors II, VII, IX, X plasma, human
  - Second International Standard
- Ferritin, human recombinant
  - Third International Standard
- Whole Blood Folate
  - First International Standard
- Thromboplastin, human recombinant, plain
  - Third International Standard

**Cytokines**
- Interleukin-5
  - First Reference Reagent
- Interleukin-7
  - First Reference Reagent
- Interleukin-9
  - First Reference Reagent
- Interleukin-11
  - First Reference Reagent
- Interleukin-12
  - First Reference Reagent
- Interleukin-13
  - First Reference Reagent
- Interleukin-15
  - First Reference Reagent
- Leukaemia Inhibitory Factor
  - First Reference Reagent
- Oncostatin M
  - First Reference Reagent
- Tumour Necrosis Factor, beta
  - First Reference Reagent
- Nerve Growth Factor
  - First Reference Reagent

**Endocrinological Substances**
- Thyroid Stimulating Hormone, human recombinant
  - First Reference Reagent

**Miscellaneous**
- Endotoxin
  - Second International Standard
- MAPREC analysis of poliovirus type 3 (Sabin)
  - First International Standard

**Discontinuations**
- Anti-rubella serum, human
  - Second International Reference Preparation
- Factor IX component of blood coagulation factors II, IX and X concentrate, human
  - Second International Reference Standard
- Oleandomycin
  - First International Standard
- Spectinomycin
  - First International Reference
- Triacytyleoleandomycin
  - First International Reference Preparation
- Viomycin
  - Second International Reference Preparation
- Endotoxin for limulus gelation tests
  - First International Standard
- Thromboplastin, human, plain
  - Second International Reference Preparation

*These reference materials are Interim Reference Reagents, as distinct from International Reference Reagents, and are established on the basis of limited data for certain rapidly developing fields where there is a need for standardization in measurement before an International Standard can be established.*
contaminating DNA deriving from continuous cell lines. Based on evidence available at that time, it was concluded that the risk associated with residual DNA is negligible when the amount of such DNA is 100 picograms or less in a single dose. A reassessment of this situation has led to DNA being considered now more as a cellular contaminant. In view of this reassessment, the recommendations have been revised so that up to 10 nanograms of residual DNA from continuous cell lines per dose of a purified product are acceptable. Of course, the purification process should be validated to demonstrate its capacity to remove cellular DNA, including spiking studies.

Requirements for acellular pertussis vaccines were also discussed by the Expert Committee. Based on the outcome of two recent international meetings, it was clear that a consensus had not yet been reached on the antigenic composition of an ideal acellular pertussis vaccine. The need for continued research to identify immune markers of protection and rigorous post-marketing surveillance of vaccine safety and effectiveness was emphasized. Because of the urgent need for guidance, the Committee agreed that the Guidelines for the production and control of the acellular pertussis component of monovalent or combined vaccines should be adopted. It also recommended that a WHO Working Group should be set up to discuss the issues and to consider how the guidelines could be extended.

Guidance concerning DNA-vaccines was also on the agenda of the meeting. This new approach to vaccination involves direct introduction into host tissue of plasmid DNA which contains the gene encoding the antigen against which an immune response is sought. Although this approach offers a number of advantages, there are several potential issues of safety. The injected DNA taken up by the cells may integrate into the host's chromosomes and cause an insertional mutagenic event. Equally, the long-term expression of a foreign antigen may result in an undesired immunopathological reaction. It is not yet known whether the use of genes encoding cytokines or co-stimulating molecules may pose extra risks. Antibodies against the injected DNA may be formed and contribute towards undesired autoimmune reactions, or the expressed antigen may itself have biological activity.

The purpose of the document Guidelines for assuring the quality of DNA vaccines is thus meant to indicate appropriate methods for the manufacture and testing of plasmid DNA vaccines and the information specific to plasmid DNA vaccines that should be included in submissions by manufacturers to national control authorities when applying for authorization of clinical trials and marketing.

Other matters of interest discussed included reverse transcriptase activity in avian cells, cytokines, reference preparations for evaluating hepatitis B, C and HIV diagnostic kits and on the standardization of gene amplification methods for the virological safety testing of blood products. The Committee recognized the great importance of the last two activities in ensuring the quality and safety of blood and blood derivatives. The possible implications of WHO's biological standardization activities on international trade as a result of the entry into force of World Trade Organization agreements were also considered.

Reference

Regulatory Matters

Irinotecan associated mortality

Japan — At least 94 patients are suspected to have died from side-effects of the anticancer drug, irinotecan, either during clinical trials or following marketing in April 1994. Topotecin® (Daichi) has been administered to some 3100 individuals and, of these, 24 patients (0.8%) have died from suspected side-effects. Campto® (Yakult) has been administered to 2330 individuals of whom 15 (0.65%) have also died because of suspected side-effects including a sudden drop in the white blood cell count. Neutropenia is known to be associated with many types of cancer chemotherapy.

The Ministry of Health and Welfare will circulate an adverse drug reaction warning to physicians and medical institutions in the near future.


HIV protease inhibitors associated with diabetes

United States of America — The Food and Drug Administration has warned physicians that protease inhibitors used to treat HIV infection may contribute to increases in blood sugar and even diabetes in HIV patients and recommends close monitoring of patient glucose levels.

The Agency has received reports of 83 cases of new or exacerbated diabetes mellitus and hyperglycaemia in HIV-infected patients taking saquinavir, indinavir, ritonavir or nelfinavir. Of the 83 patients, 27 were reported to need hospitalization, including six life-threatening cases. Five cases resulted in ketoacidosis, a serious diabetes-related condition that is characterized by a fruity mouth odour, nausea, vomiting, dehydration, weight loss, confusion and, if untreated, coma or death.

The FDA emphasizes that HIV patients on protease inhibitor therapy should be informed of the warning signs of hyperglycaemia and diabetes, which are increased thirst and hunger, unexpected weight loss, increased urination, fatigue, and dry, itchy skin. The symptoms in reported cases occurred, on average, approximately 76 days from commencement of protease inhibitor therapy, but in some cases as early as four days. None the less, the FDA points out that the benefit of these drugs to patients suffering from HIV infection far outweighs the various risks.


Valvular heart disease associated with fenfluramine and phentermine

United States of America — The Food and Drug Administration has alerted physicians to reports of valvular heart disease in women treated for obesity with a combination of fenfluramine and phentermine. The drugs were approved individually more than 20 years ago for single-drug, short-term obesity therapy. Recently, however, they have been widely used “off-label” in combination, for long-term management of obesity (1).

The FDA has received reports of 33 cases of unusual abnormalities of the mitral, aortic, and tricuspid heart valves in women between 30 and 72 years of age with no previous cardiac disease who have been taking fenfluramine and phentermine for between one and 28 months.

The valve damage was characterized by a glistening white macroscopic appearance and microscopic endothelial fibrons were seen. The damage may be related to high circulating serotonin concentrations since both fenfluramine and phentermine raise serotonin concentrations (2). As of July 1997, surgical intervention to replace a damaged valve had been required in six patients (3).

A study carried out on valvular disease in women will be published in the New England Journal of Medicine later this year.

References

3. SCRIP Number 2250, 18 July 1997.
Withdrawal of antidiarrhoeal paediatric product

France — The Medicines Agency has taken restrictive action against two antidiarrhoeal products, a paediatric formulation containing tilbroquinol (IntetrixP®, Beaufour) and a combination product containing tilbroquinol and tiliquinol (Intetrix®, Beaufour) because of potential hepatotoxicity.

The approved indications were acute diarrhoea of infectious origin without invasive phenomena, and intestinal amoebiasis. The product may also be used for treatment of dysenteric amoebiasis in combination with a tissue amoebicide, or as monotherapy in healthy carriers contaminated with intra-luminal amoebae. Eight cases of asymptomatic increased liver transaminases were reported among 12 healthy volunteers enrolled in a clinical study of Intetrix®, and 10 subsequent cases of liver disorder were identified by the national pharmacovigilance system.

Although no cases were reported for the paediatric formulation (1), the manufacturer has suspended sales of IntetrixP® and batches have been recalled. The therapeutic indications of Intetrix® are now restricted to the treatment of intestinal amoebiasis in adults.

The manufacturer has informed WHO that both products have been marketed in various countries throughout the world (2).

References

2. Dear Doctor letter from Beaufour Laboratories and communication to WHO of 30 July 1997.

Dangerous products promoted on the Internet

United States of America — The Food and Drug Administration has issued a warning to consumers concerning unapproved products offered for sale on the Internet which could cause significant health risks. The products in question are an abortion kit and a self-sterilization kit.

The abortion kit provides a combination of drugs which are not approved by the FDA to terminate pregnancy. These drugs, without a physician's supervision, could cause heavy vaginal bleeding and even death. Birth defects in the fetus could also occur if the product failed and pregnancy was carried to term. The sterilization kit contains quinacrine hydrochloride (INN: mepacrine) which can cause a pregnancy to become ectopic or abnormal, or cause permanent damage to a woman's re-productive organs. Despite these dangers, the kits are promoted as "scientific and without risk".


Health risks of herbal products containing ephedrine

Canada and United States of America — The Canadian Health Department warns consumers not to take dietary supplements containing ephedrine unless the product label carries a drug identification number (DIN), since close to 20 deaths reported in the United States have been linked to preparations containing this herb or its active constituent (1). In 1996, the United States Food and Drug Administration had issued a similar warning following reports that ephedrine supplements were being taken to reduce weight, increase energy to enhance body-building and — in large doses — as a euphoric.

A review has now been made of more than 800 reports of adverse effects received by the FDA (2), which include high blood pressure, irregularities in heartbeat, insomnia, nervousness, tremors, headaches, seizures, heart attacks, stroke and even death. Most events occurred in otherwise healthy individuals using the products for weight control and increased energy and obtaining them from non-approved outlets including fitness centres.

It is proposed that the amount of ephedrine alkaloids in these products should be controlled and marketing prohibited of products containing more than 8 mg of ephedrine alkaloids in the amount ingested in a 6-hour period or 24 mg in the total daily intake. It will also require warning labels and instructions to consumers not to use the product for more than 7 consecutive days.

Ephedrine alkaloids are amphetamine-like compounds with potentially powerful stimulant effects on the nervous system and heart and certain individuals should avoid their use. In supplements, they are usually derived from a herb known as ma huang, Chinese ephedra, ephedra sinica, epitonin or ephedrine. Other botanical sources include *Sida cordifolia*. 
Photoallergic and phototoxic reactions associated with fibrates

Germany — The Federal Institute of Drugs and Medical Devices has decided to alter the package inserts and information for health professionals on products containing fenofibrate, gemfibrozil, clofibric acid, clofibrate, etofylline clofibrate, etofibrate and bezafibrate. If users of these products are exposed to real or artificial sunlight, the skin may become reddened and itchy, and blisters or nodules may appear. This adverse effect may occur at any time — even after complication-free use of many months duration.

Contraindications now include known hypersensitivity, skin reactions following exposure to solar radiation, and concomitant administration with another product containing a substance of the fibrate group. In the case of fenofibrate, concomitant use of ketoprofen is also contraindicated.

Reference: Communication from the Federal Institute of Drugs and Medical Devices to WHO dated 4 July 1997.

First-year safety reports with triple component pertussis vaccine

Sweden — The Medical Products Agency has analysed adverse reaction reports for the first year of use (1996) of a combined pertussis vaccine (Infanrix®, SmithKline Beecham). The vaccine contains pertussis toxin, filamentous haemagglutinin and pertactin.

Of the 89 reports received, 52 were of a general nature, including 25 cases of fever and 18 skin reactions. Other reactions included prolonged crying episodes, restlessness, apparent pain, fever, cramps and 2 cases of muscle hypotonia.

Additionally, there were 18 cases of hypotonic hyporesponsive episodes (HHEs) which usually occurred on the first day following vaccination. When this happened, the children became suddenly pale, loose, unresponsive and impossible to communicate with, often for hours. The mechanism behind this reaction is unknown but seems to be harmless, although it was an unpleasant experience for the families concerned. The Agency has stated that it did not expect this vaccine to cause HHE.

Essential Drugs

WHO Model Formulary

As described in previous issues of this journal, work is now under way on the WHO Model Formulary, and draft texts will be published regularly to obtain comments on the material proposed for publication. Observations concerning the following section related to anthelminthics should be addressed to: Drug Selection and Information (DSI), Division of Drug Management & Policies, World Health Organization, 1211 Geneva 27, Switzerland.

Antiprotozoal drugs

Drugs used in amoebiasis

Amoebic dysentery, caused by *Entamoeba histolytica*, occurs when protozoan parasites invade the wall of the large intestine. Trophozoites may also invade the appendix and terminal ileum, or may reach the liver and produce an amoebic liver abscess. Extension of hepatic lesions may reach the right chest, the peritoneum and the pericardium. Less commonly, the lesion extends through the skin, producing a sinus and cutaneous lesion. Rarely, *E. histolytica* trophozoites cause brain abscesses. Pregnant women and individuals who are malnourished or immunocompromised are most vulnerable.

The incidence of amoebiasis falls as sanitary measures are introduced. Chlorination of water does not destroy amoebic cysts but adequate filtration will remove them. A weak solution of iodine is a potent cysticide.

Luminal amoebicides are active primarily against organisms in the colon, and systemic amoebicides are active against organisms responsible for invasive disease. In non-endemic areas, symptomless carriers should be treated with a luminal amoebicide, which will reduce the risk of transmission and protect the patient from invasive amoebiasis. Diloxanide furoate is most widely used, but other compounds, including clefamide, etofamide and teclozan, are also effective.

All patients with invasive amoebiasis require treatment with a systemically active compound followed by a luminal amoebicide in order to eliminate any surviving organisms in the colon. Combined preparations are useful. The pathology and clinical expression of amoebiasis vary from region to region and drug regimens should consequently be devised on the basis of local experience.

The availability of metronidazole and several other 5-nitroimidazoles, including ornidazole, tinidazole and secnidazole, has made the management of invasive amoebiasis simpler and safer. Parenteral formulations of metronidazole, ornidazole and tinidazole are available for patients too ill to take drugs by mouth.

In severe cases of amoebic dysentery, tetracycline given in combination with a systemic amoebicide lessens the risk of overinfection, intestinal perforation and peritonitis. Hepatic abscesses should be lanced by needle aspiration if severe hepatic pain and tenderness indicate that rupture is imminent.

**DILOXANIDE**

*Luminal amoebicide*

Tablet: 500 mg of diloxanide furoate

*Uses*: Treatment of asymptomatic carriers in non-endemic areas. Eradication of residual amoebae in the colonic lumen following treatment of invasive disease with other drugs.

*Dosage*: *Adults*: 500 mg 3 times daily for 10 days. *Children*: 20 mg/kg daily in 3 divided doses for 10 days. Treatment is regarded as successful if stools remain free of *E. histolytica* for one month. Several specimens should be taken in evaluating the response to treatment.
**Precautions:** In pregnancy, treatment is best deferred until after the first trimester.

**Adverse effects:** Mild gastrointestinal symptoms, particularly flatulence, may be troublesome. Pruritus and urticaria can also occur.

**Drug interactions:** These will appear in tabulated form in the appendix of the published edition of the WHO Model Formulary.

**Drugs used in giardiasis**

*Giardia intestinalis* is a flagellated protozoan parasite which frequently coexists with *E. histolytica* and is usually transmitted in drinking-water which contains cysts. These can be removed by water filtration. Many carriers are symptomless, but others lose weight and complain of diarrhoea or gastro-intestinal discomfort. Extensive infections result in intestinal malabsorption and impaired growth in children. Severe symptoms are more likely to occur in patients who are malnourished, hypochlorhydric or immunocompromised.

Treatment with tinidazole in a single dose or with another 5-nitroimidazole such as metronidazole is highly effective and should be offered when practicable to all infected patients. Family and institutional contacts should also be treated. Larger epidemics are difficult to eradicate because of the high proportion of symptomless carriers and because excreted cysts can survive for long periods outside the human host.

**METRONIDAZOLE**

*Antiprotozoal agent*

- **Tablet:** 200 – 500 mg
- **Injection:** 500 mg in 100-ml vial
- **Oral suspension:** 200 mg (as benzoate)/5ml

**Uses:** Treatment of invasive amoebiasis and giardiasis. Treatment of asymptomatic carriers in non-endemic areas if no luminal amoebicide is available, although it is less effective.

**Dosage:** Metronidazole should be administered with or immediately after food. Various dosage regimens are used, and definitive recommendations should be based on local experience.

**Invasive amoebiasis**

*Adults and children:* 30 mg/kg daily in 3 oral divided doses after meals for 8 –10 days, or intravenously in 3 divided injections daily until the patient is able to take oral formulations. The patient should subsequently receive a luminal amoebicide to eliminate surviving organisms in the colon.

**Giardiasis**

*Adults:* 2 g once daily for 3 days.

*Children:* 15 mg/kg daily in divided doses for 5–10 days.

**Contraindications:** Known hypersensitivity; first trimester pregnancy; chronic alcohol dependence.

**Precautions:** Peripheral neuropathy, ataxia or other signs of central nervous system dysfunction warrant prompt discontinuation.

**Adverse effects:** Commonly, mild symptoms of headache, gastrointestinal irritation and a persistent metallic taste. Less frequently, drowsiness, rashes, and brownish-red darkening of urine may occur. Rarely, stomatitis and candidiasis, reversible leukopenia, and sensory peripheral neuropathy occur. Disulfiram-like effects such as abdominal pain, vomiting, flushing and headache may occur if alcohol is consumed.

**Drug interactions:** These will appear in tabulated form in the appendix of the published edition of the WHO Model Formulary.

**Drugs used in leishmaniasis**

Protozoa of the *Leishmania spp* are responsible for several clinically distinctive diseases characterized by chronic inflammatory infiltration, focal necrosis and fibrosis. In some, the lesions are localized at the point of inoculation but in others the parasite becomes widely disseminated. The parasite is transmitted from animals by sandflies.

Leishmania species differ in their sensitivity to chemotherapy. Visceral leishmaniasis, caused by parasites of the *Leishmania donovani* complex, is usually responsive initially to the pentavalent antimonial compounds, meglumine antimoniate or sodium stibogluconate. Both dosage and duration of treatment need to be adjusted according to the clinical response. Patients are considered to be clinically cured when no parasites are detected in splenic or bone marrow aspirates. However, biopsies should be carried out again after 3 and 12 months since relapse is frequent. Antimonials combined with allopurinol, pentamidine and amphotericin B have been used with success in
patients in relapse who have become unresponsive to antimonials alone.

Cutaneous leishmaniasis, caused by *L. major*, *L. tropica*, *L. mexicana* and *L. peruviana*, is responsive to intralesional injections of antimonial compounds. Mild lesions can often be left to heal spontaneously. However, it is preferable to treat *L. tropica* infections with a view to reducing transmission since humans seem to be the only host. When the lesion is inflamed or ulcerated or when obstruction of lymphatic drainage or destruction of cartilage creates a risk of serious disfigurement or disability, antimonials should be administered systematically as well as locally. Infections due to *L. braziliensis*, and the less common *L. panamensis*, respond to antimonial treatment. *L. aethiopica* is less responsive at conventional doses and the sores should be left to heal spontaneously if there is no evidence of cutaneous involvement. *L. guyanensis* infections should be treated with pentamidine.

Mucocutaneous leishmaniasis can cause permanent disfiguring lesions, and *L. braziliensis* infections, in particular, are associated with the added risk of espundia. The latter usually responds to antimonials and, when relapses occur, more extended courses of treatment are often successful. Patients who still fail to respond should receive amphotericin B or pentamidine, although neither treatment is highly satisfactory.

Because of resistance to antimonials, *L. aethiopica* infections should be treated with pentamidine from the outset until complete healing occurs. Emergency use of corticosteroids may be needed to control pharyngeal or tracheal oedema produced by severe inflammation resulting from antigens liberated from dead parasites during the early phase of treatment. Antibiotics may also be needed to treat secondary infections, and plastic surgery offers the only means of ameliorating disfiguring scars. Diffuse cutaneous leishmaniasis is usually treated with antimonial compounds, but relapses must be expected and repeated courses of pentamidine may be needed until clinical immunity becomes established.

Safe use in pregnancy of antimonial compounds, pentamidine or amphotericin B has not been established and they should be used only when the benefits to the mother outweigh the risks to the fetus. However, in visceral leishmaniasis, which is potentially fatal, treatment should always be given without delay.

MEGLUMINE ANTIMONIATE & SODIUM STIBOGLUCONATE

*Antiprotozoal agent*

*Injection*: equivalent of 85 mg/ml meglumine antimoniate or 100 mg/ml sodium stibogluconate of antimony (Sb\(^{5+}\)) in 5-ml ampoule

*Uses:*

Visceral leishmaniasis; cutaneous leishmaniasis (except for *L. aethiopica* infections, which are unresponsive); diffuse cutaneous leishmaniasis due to *L. amazonensis*, cutaneous and mucocutaneous leishmaniasis due to *L. braziliensis*.

*Dosage:*

Intramuscular doses are expressed in terms of the equivalent amount of pentavalent antimony (Sb\(^{5+}\)). All doses, which are weight related, are suitable for both adults and children.

Visceral leishmaniasis

Injection of 20 mg of Sb\(^{5+}\)/kg i.m. daily for a minimum of 20 days. Treatment should be continued until no parasites are detected in consecutive splenic aspirates taken at 14-day intervals.

Patients who relapse following the first course of treatment should be retreated immediately using the same daily dosage.

Cutaneous leishmaniasis except *L. aethiopica*.

*Local therapy*: Injection of 1–3 ml into the base of the lesion, repeated once or twice if no response is apparent, at intervals of 1 to 2 days.

*Systemic therapy*: Injection of 10–20 mg Sb\(^{5+}\)/kg i.m. daily until lesion is healed and for at least 4 weeks. Relapse is usually associated with inadequate dosage or interrupted treatment. Should relapse occur following a full course of treatment, pentamidine should be used.

*Mucocutaneous leishmaniasis (L. braziliensis)*:

Injection of 20 mg Sb\(^{5+}\)/kg daily i.m. until slit-skin smears are negative and for at least 4 weeks. In the event of toxicity or inadequate response, 10–15 mg Sb\(^{5+}\)/kg should be administered every 12 hours for the same period. Patients who relapse should be retreated for at least twice as long. Those who are unresponsive should receive amphotericin B or pentamidine.
Diffuse cutaneous leishmaniasis (L. amazonensis): Injection of 20 mg Sb\(^{5+}\)/kg daily i.m. for several months after clinical improvement occurs. Relapse must be expected until immunity develops.

**Contraindications:** Severe kidney, heart or liver disorders.

**Precautions:** Provision of a protein-rich diet throughout treatment is essential and, where possible, iron and other specific deficiencies should be corrected beforehand. When possible, monitor throughout the electrocardiogram, renal and hepatic functions and reduce dosage in case of abnormalities.

Safe use in pregnancy has not been established. However, in visceral leishmaniasis, which is potentially fatal, treatment should always be given without delay.

**Adverse effects:** Reversible dose-dependent electrocardiographic changes; hepatic and renal function impairment; occasionally, headache, malaise, dyspnoea, skin rashes, facial oedema and abdominal pain.

**Drug interactions:** These will appear in tabulated form in the appendix of the published edition of the WHO Model Formulary.

**PENTAMIDINE**

Antiprotozoal agent

**Powder for injection:** 200 mg, 300 mg of pentamidine isetionate in vial

**Uses:** In patients who are unresponsive to or intolerant of antimony compounds, in cutaneous leishmaniasis, diffuse cutaneous leishmaniasis and mucocutaneous leishmaniasis due to *L. aethiopica* and *L. braziliensis* unresponsive to antimony compounds; cutaneous leishmaniasis due to *L. guyanensis*.

**Dosage:** Deep intramuscular injection is preferred. Intravenous infusions must be delivered over a period of not less than 60 minutes to avert the risk of cardiovascular collapse. All doses, which are weight related, are suitable for both adults and children.

**Visceral leishmaniasis:** Injection of 4 mg/kg three times a week for 5 to 25 weeks, or longer, until no parasites are detected in two consecutive splenic aspirates taken 14 days apart.

**Cutaneous leishmaniasis (L. aethiopica and L. guyanensis):** Injection of 3–4 mg/kg once or twice a week until the lesion is no longer visible. Relapse is unusual.

**Diffuse cutaneous leishmaniasis (L. aethiopica):** Injection of 3–4 mg/kg once a week, continued for at least 4 months after parasites are no longer detectable in slit-skin smears. Relapse frequently occurs during the first few months before immunity is established.

**Mucocutaneous leishmaniasis (L. braziliensis and L aethiopica):** Injection of 4 mg/kg 3 times a week for 5 to 25 weeks, or longer, until the lesion is no longer visible.

**Contraindications:** Known hypersensitivity and severe renal impairment.

Safe use in pregnancy has not been established. However, in visceral leishmaniasis, which is potentially fatal, treatment should always be given without delay.

**Precautions:** Because of the risk of hypotension and syncope, all patients should remain supine and under observation for at least 30 minutes after each injection. When possible, monitor blood pressure, full blood count and serum creatinine at regular intervals throughout treatment and blood glucose daily. In immunodeficient patients, interrupt or discontinue treatment if acute deterioration of bone marrow, renal or pancreatic function occurs.

**Adverse effects:** Frequently, completely reversible mild nephrotoxicity, acute hypotenstion and syncope may occur after rapid i.v. injection. Pancreatic damage resulting initially in hypoglycaemia and finally in insulin insufficiency may lead to permanent insulin-dependent diabetes.

Other effects include hypocalcaemia, gastrointestinal irritation, confusion, hallucinations, cardiac dysrhythmias, local induration and occasionally, sterile abscess. Rarely, thrombocytopenia, leukopenia, abnormal hepatic function tests, and Stevens–Johnson syndrome have been reported.

**Drug interactions:** These will appear in tabulated form in the appendix of the published edition of the WHO Model Formulary.
AMPHOTERICIN B
Antiprotozoal agent
Powder for injection: 50 mg in vial

Uses: Visceral and mucocutaneous leishmaniasis unresponsive to pentavalent antimony compounds.

Dosage: Adults: A starting dose of 5–10 mg is incremented by 5 to 10 mg daily to the maximum of 0.5–1 mg/kg. This is then administered on alternate days. A total cumulative dose of 1–3 g is usually required.

Contraindications: Known hypersensitivity.

Safe use in pregnancy has not been established and amphotericin B should be used only when the benefits to the mother outweigh the risks to the fetus.

Precautions: Close medical supervision is required throughout treatment. Closely monitor renal function, serum potassium levels and blood count.

Adverse effects: Drug infusion may cause anaphylaxis. Frequently, chills, fever, and vomiting occur. Occasionally, flushing, muscle and joint pains, headache and anorexia are particularly marked in the first days of treatment, and partially reversible deterioration of renal function, as well as progressive normochromic anaemia indicative of bone-marrow depression have been reported. Less commonly, selective leukopenia and thrombocytopenia, nerve palsies, impaired vision, tinnitus and difficult micturition also occur.

Drug interactions: These will appear in tabulated form in the appendix of the published edition of the WHO Model Formulary.

MELARSOPROL
Antiprotozoal agent
Injection: 3.6% solution in propylene glycol

Uses: Confirmed cases of T. b. gambiense or T. b. rhodesiense infection with meningoencephalitic involvement.

Dosage: Several treatment regimens for adults and children are currently used in the absence of clear evidence that one is better than another. They each comprise three or four series of daily injections with intervening periods of 7 to 10 days and are set out in the table on page 150.

Contraindications: Pregnancy.

Precautions: Hospitalization and close medical supervision are required throughout treatment. Episodes of reactive encephalopathy may require suspension of treatment. Intercurrent infections such as pneumonia and malaria should be treated before melarsoprol is administered. Where possible, malnutrition should be corrected with a protein-rich diet.

Drugs used in trypanosomiasis
African trypanosomiasis, or sleeping sickness, is a protozoan infection transmitted by Glossina spp (tsetse flies). Two subspecies of Trypanosoma brucei — gambiense and rhodesiense — produce distinctive clinical forms of the disease. Early-stage infection due to T. b. rhodesiense is characterized by a transient indurated weal or chancre. Invasion of lymphatics and blood vessels occurs a few days later, causing regional or generalized lymphadenopathy and widespread systemic dissemination. Intermittent fevers accompanied by malaise, headaches, joint pains, pruritus, skin rashes and oedema are followed by normochromic or hypochromic anaemia, and a pancarditis ultimately resulting in dysrhythmias and heart failure. Other signs of organic involvement are common. In men, endocrine involvement can cause impotence and, in women, menstruation disorders, sterility, abortion and premature delivery, as well as stillbirth or perinatal death. Signs of meningo-encephalitis develop within a few weeks and early symptoms include insomnia, neurological disorders and mental changes. Apathy and somnolence supervene and untreated patients ultimately die from malnutrition, intercurrent infection or deepening coma. Symptoms of African trypanosomiasis caused by T. b. gambiense are similar, but take several months or even years to develop.

Efornithine has been shown to be both effective and considerably less toxic than melarsoprol in patients with meningoencephalopathy resulting from T. b. gambiense trypanosomiasis. Efornithine alone is ineffective in T. b. rhodesiense infections.
Adverse effects: Serious complications such as reactive encephalopathy characterized by headache, tremor, slurring of speech, convulsions and ultimately coma. Frequent severe adverse effects include myocardial damage, albuminuria and hypertension. Less commonly, hypersensitivity reactions, agranulocytosis, or dose-related renal and hepatic dysfunction can occur during later phases of treatment. Less serious adverse effects include hyperthermia, urticaria, headache, diarrhoea and vomiting.

Drug interactions: These will appear in tabulated form in the appendix of the published edition of the WHO Model Formulary.

PENTAMIDINE
Antiprotozoal agent
Powder for injection: 200 mg of pentamidine isetionate in vial

Uses: T. b. gambiense infections with a view to obtaining a radical cure in the haemolymphatic stage of African trypanosomiasis or clearing the blood and lymph of trypanosomes prior to treatment with melarsoprol.

Dosage: The powder for injection should be reconstituted with “water for injection”.

Adults and children:
For early disease: 4 mg/kg, in each of a total of 7–10 intramuscular injections, administered at a rate of one per day or one every other day. For late disease: see table on page 150.

Contraindications: Known hypersensitivity; severe renal impairment; T. b. rhodesiense trypanosomiasis, since primary resistance to pentamidine has been observed.

Precautions: Cerebrospinal fluid should always be examined before treatment since pentamidine is not likely to be effective if the leukocyte count is greater than 5 cells/mm, the total protein content is greater than 37 mg/100 ml, or if trypanosomes can be detected in centrifuged deposits. Use in pregnancy can induce abortion. However, pentamidine should not be withheld during pregnancy even if there is evidence of meningoencephalitic involvement since melarsoprol should not be used.

Because of the risk of hypotension and syncope all patients should remain supine and under observation for at least 30 minutes after each injection.

When possible, monitor blood pressure, full blood count and serum creatinine at regular intervals throughout treatment and blood glucose daily. In immunodeficient patients, interrupt or discontinue treatment if acute deterioration of bone marrow, renal or pancreatic function occurs.

Adverse effects: Frequently, completely reversible mild nephrotoxicity, acute hypotension and syncope after rapid intravenous injection, pancreatic damage resulting initially in hypoglycaemia and finally in insulin insufficiency which may lead to permanent insulin-dependent diabetes. Other effects include hypocalcaemia, gastrointestinal troubles, confusion, hallucinations, cardiac dysrhythmias, local induration and, occasionally, sterile abscess. Rarely, thrombocytopenia, leucopenia, abnormal hepatic function tests, and Stevens–Johnson syndrome have been reported.

Drug interactions: These will appear in tabulated form in the appendix of the published edition of the WHO Model Formulary.

SURAMIN SODIUM
Antiprotozoal agent
Powder for injection: 1 g in vial

Uses: T. b. gambiense and T. b. rhodesiense trypanosomiasis with a view to obtaining a radical cure in the haemolymphatic stage of the disease or clearing the blood and lymph of trypanosomes prior to treatment with melarsoprol.

Dosage: Doses for both adults and children in mg/kg for radical cure (A) and for administration before melarsoprol treatment (B) are shown in the table below:

<table>
<thead>
<tr>
<th>Day</th>
<th>1</th>
<th>3</th>
<th>5</th>
<th>11</th>
<th>17</th>
<th>23</th>
<th>30</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment A</td>
<td>5</td>
<td>10</td>
<td>20</td>
<td>20</td>
<td>20</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>Treatment B</td>
<td>5</td>
<td>10</td>
<td>20</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

All doses should be administered by slow intravenous injection of a 10% w/v solution in “water for injection” to be used within 30 minutes of preparation. The first injection should be given with particular caution.

Contraindications: Previous anaphylactic reactions or sensitivity to suramin; pregnancy (see precautions page 150–151); children less than 10
years old; elderly or infirm patients with impaired liver or renal function; total blindness — unless required for relief from intensely itchy lesions.

**Precautions:** Suramin is extremely toxic and should always be given under medical supervision in a hospital. A satisfactory food and fluid intake should be maintained throughout treatment. Urine samples should be taken before and during treatment to detect the presence of albumin. Moderate albuminuria indicates that the dose should be reduced but heavy albuminuria with the passage of casts indicates the need for immediate discontinuation of treatment.

### Treatment schedule for African trypanosomiasis with meningoencephalitic involvement.

<table>
<thead>
<tr>
<th>Day</th>
<th>Drug</th>
<th>Dose (mg/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>For <em>T. b. rhodesiense</em> infection, as used in Kenya and Zambia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>suramin</td>
<td>5.00</td>
</tr>
<tr>
<td>3</td>
<td>suramin</td>
<td>10.00</td>
</tr>
<tr>
<td>5</td>
<td>suramin</td>
<td>20.00</td>
</tr>
<tr>
<td>7</td>
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</tr>
<tr>
<td>8</td>
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<td>0.72</td>
</tr>
<tr>
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</tr>
<tr>
<td>16</td>
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</tr>
<tr>
<td>17</td>
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<td>1.80</td>
</tr>
<tr>
<td>18</td>
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</tr>
<tr>
<td>25</td>
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<td>2.90</td>
</tr>
<tr>
<td>26</td>
<td>melarsoprol</td>
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</tr>
<tr>
<td>27</td>
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<td>3.60</td>
</tr>
<tr>
<td>34</td>
<td>melarsoprol</td>
<td>3.60</td>
</tr>
<tr>
<td>35</td>
<td>melarsoprol</td>
<td>3.60</td>
</tr>
<tr>
<td>36</td>
<td>melarsoprol</td>
<td>3.60</td>
</tr>
</tbody>
</table>

For *T. b rhodesiense* infection, as used in Uganda and the United Republic of Tanzania

<table>
<thead>
<tr>
<th>Day</th>
<th>Drug</th>
<th>Dose (mg/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>suramin</td>
<td>5.00</td>
</tr>
<tr>
<td>3</td>
<td>suramin</td>
<td>10.00</td>
</tr>
<tr>
<td>5</td>
<td>melarsoprol</td>
<td>1.80</td>
</tr>
<tr>
<td>6</td>
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<td>7</td>
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</tr>
<tr>
<td>14</td>
<td>melarsoprol</td>
<td>2.56</td>
</tr>
<tr>
<td>15</td>
<td>melarsoprol</td>
<td>2.90</td>
</tr>
<tr>
<td>16</td>
<td>melarsoprol</td>
<td>3.26</td>
</tr>
<tr>
<td>23</td>
<td>melarsoprol</td>
<td>3.60</td>
</tr>
<tr>
<td>24</td>
<td>melarsoprol</td>
<td>3.60</td>
</tr>
<tr>
<td>25</td>
<td>melarsoprol</td>
<td>3.60</td>
</tr>
</tbody>
</table>

For *T. b gambiense* infection, as used in Cote d’ Ivoire

<table>
<thead>
<tr>
<th>Day</th>
<th>Drug</th>
<th>Dose (mg/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>pentamidine i.m.</td>
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</tr>
<tr>
<td>2</td>
<td>pentamidine i.m.</td>
<td>4.00</td>
</tr>
<tr>
<td>4</td>
<td>melarsoprol</td>
<td>1.20</td>
</tr>
<tr>
<td>5</td>
<td>melarsoprol</td>
<td>2.40</td>
</tr>
<tr>
<td>6</td>
<td>melarsoprol</td>
<td>3.60</td>
</tr>
<tr>
<td>17</td>
<td>melarsoprol</td>
<td>1.20</td>
</tr>
<tr>
<td>18</td>
<td>melarsoprol</td>
<td>2.40</td>
</tr>
<tr>
<td>19</td>
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<tr>
<td>20</td>
<td>melarsoprol</td>
<td>3.60</td>
</tr>
<tr>
<td>30</td>
<td>melarsoprol</td>
<td>1.20</td>
</tr>
<tr>
<td>31</td>
<td>melarsoprol</td>
<td>2.40</td>
</tr>
<tr>
<td>32</td>
<td>melarsoprol</td>
<td>3.60</td>
</tr>
<tr>
<td>33</td>
<td>melarsoprol</td>
<td>3.60</td>
</tr>
</tbody>
</table>
Suramin may be given to pregnant women with *T. b. rhodesiense* trypanosomiasis even if there is evidence of meningoencephalitic involvement, since melarsoprol must not be given before delivery.

**Adverse effects:** Direct toxic effects require immediate withdrawal. Rarely, potentially fatal loss of consciousness may occur during the first injection. Heavy albuminuria, stomal ulceration, exfoliative dermatitis, severe diarrhoea, prolonged high fever and prostration may occur. Lesser, but common, symptoms include tiredness, anorexia, malaise, polyuria.

**Drug interactions:** These will appear in tabulated form in the appendix of the published edition of the WHO Model Formulary.

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**EFLORNITHINE**

*Antiprotozoal agent*

*Injection:* 200 mg of eflornithine hydrochloride/ml solution in 100-ml ampoule

*Uses:* *T. b. gambiense* trypanosomiasis in both the early and the late stages.

*Dosage:*

**Adults and children:** A dose of 100 mg/kg should be administered, by infusion over a period of 45 minutes, every 6 hours for at least 14 days.

**Contraindications:** Pregnancy and lactation.

**Precautions:** Hospitalization with close supervision required throughout treatment. Blood and lymph node aspirates required daily until trypanosome negative for two consecutive days. Thereafter, weekly aspirate examination throughout treatment. Cerebrospinal fluid examination for determination of leukocytes, total protein content and trypanosomes required after a complete course of treatment, and thereafter at 1, 3, 6, 12 and 24 months.

Parasitological evidence of relapse requires a further course of therapy.

**Adverse effects:** Most commonly reported effects are diarrhoea, anaemia, leukopenia, thrombocytopenia, convulsions and impaired hearing. Less commonly reported effects, which are reversible on drug withdrawal, are vomiting, anorexia, alopecia, abdominal pain, headache, facial oedema, eosinophilia and dizziness.

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**BENZNIDAZOLE**

*Antiprotozoal agent*

*Scored tablet:* 100 mg

*Uses:* Acute American trypanosomiasis (Chagas disease).

*Dosage:*

**Adults:** 5 – 7 mg/kg orally in two divided doses daily for 60 days.

**Children (up to 12 years):** 10 mg/kg orally in two divided doses daily for 60 days.

**Contraindications:** Alcohol; first trimester pregnancy.

**Precautions:** Patients with hepatic, renal or haematological insufficiency should be kept under close medical supervision. The blood count, especially leukocytes, should be monitored throughout treatment.
**Adverse effects:** Frequently, mild rashes and nausea may occur. Treatment must be discontinued in the case of fever, purpura or dose-related paraesthesia or symptoms of peripheral polyneuritis. More serious adverse effects include leukopenia and, rarely, agranulocytosis or exfoliative dermatitis.

**Drug interactions:** These will appear in tabulated form in the appendix of the published edition of the WHO Model Formulary.

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**NIFURTIMOX**

*Antiprotozoal agent*

*Tablet:* 30 mg, 120 mg, 250 mg

**Uses:** Acute American trypanosomiasis (Chagas disease).

**Dosage:**

*Adults:* 8–10 mg/kg orally in three divided daily doses for 90 days.

*Children:* 15 –30 mg /kg orally in four divided daily doses for 90 days.

**Contraindications:** First trimester pregnancy.

**Precautions:** Gastrointestinal irritation (reduced with simultaneous use of aluminium hydroxide). Alcohol avoidance to reduce incidence and severity of adverse effects. History of convulsions (close medical supervision). Reduction of daily doses if weight loss, neurological disturbances or other manifestations of intolerance occur.

**Adverse effects:** Dose-related reversible effects frequently occur and include anorexia, nausea, vomiting, gastric pain, insomnia, head-ache, vertigo, excitability, myalgia, arthralgia and convulsions. Seizures may be symptomatically controlled with anticonvulsants. Discontinuation of treatment may be necessary in the case of peripheral polyneuritis.

**Drug interactions:** These will appear in tabulated form in the appendix of the published edition of the WHO Model Formulary.
ATC/DDD Classification (temporary)

The following temporary classifications were agreed at a meeting of the International Working Group on ATC/DDD Classification which took place from 29 to 30 April 1997 in Geneva. Comments on, or objections to, the classification should be forwarded to the WHO Collaborating Centre for Drug Statistics Methodology, Sven Oftedals Vei 10, 0518, Oslo, Norway (telephone: 00 47 22 16 9810, fax: 0047 22 16 9818) before 15 November 1997. Provided there have been no objections, the classification will come into force on 1 January 1998. A final list of classifications will be published subsequently in this journal.

<table>
<thead>
<tr>
<th>ATC Level</th>
<th>INN/common name</th>
<th>ATC code</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>New ATC levels:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peripherally acting antiobesity products</td>
<td></td>
<td>A08A B</td>
</tr>
<tr>
<td>Drugs used in erectile dysfunction</td>
<td></td>
<td>G04B E</td>
</tr>
<tr>
<td>Drugs used in benign prostatic hypertrophy</td>
<td></td>
<td>G04C</td>
</tr>
<tr>
<td>Alpha-adrenoceptor blocking agents</td>
<td></td>
<td>G04C A</td>
</tr>
<tr>
<td>Testosterone-5-alpha reductase inhibitors</td>
<td></td>
<td>G04C B</td>
</tr>
<tr>
<td>Other drugs used in benign prostatic hypertrophy</td>
<td></td>
<td>G04C X</td>
</tr>
<tr>
<td>Medical gases</td>
<td></td>
<td>V03A N</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>ATC code changes:</th>
<th>previous ATC</th>
<th>new ATC</th>
</tr>
</thead>
<tbody>
<tr>
<td>alfuzosin</td>
<td>G04B X02</td>
<td>G04C A01</td>
</tr>
<tr>
<td>alprostadil</td>
<td>G04B X05</td>
<td>G04B E01</td>
</tr>
<tr>
<td>dacarbazine</td>
<td>L01X X13</td>
<td>L01A X04</td>
</tr>
<tr>
<td>finasteride</td>
<td>G04B X04</td>
<td>G04C B01</td>
</tr>
<tr>
<td>papaverine</td>
<td>A03A D01</td>
<td>G04B E02</td>
</tr>
<tr>
<td>* (formulations for intracavernous use)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>papaverine, comb.</td>
<td>A03A D51</td>
<td>G04B E52</td>
</tr>
<tr>
<td>* (in combination with phentolamine)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>pygeum africanum</td>
<td>G04B X07</td>
<td>G04C X01</td>
</tr>
<tr>
<td>serenoa repens</td>
<td>G04B X09</td>
<td>G04C X02</td>
</tr>
<tr>
<td>tamsulosin</td>
<td>G04B X08</td>
<td>G04C A02</td>
</tr>
<tr>
<td>yohimbeg</td>
<td>V03A X01</td>
<td>G04B E04</td>
</tr>
</tbody>
</table>

| New ATC 5th level codes:                      |              |         |
| atorvastatin                                   | C10A A05     |         |
| capsaicin                                      | N01B X04     |         |
| dodecafluoropentane                            | V08D A03     |         |
| dolasetron                                     | A04A A04     |         |
| donepezil                                      | N07A A05     |         |
| ferric acetyl transferrin                      | B03A B08     |         |

* additional information
### New ATC 5th level codes (continued)

<table>
<thead>
<tr>
<th>INN/common name</th>
<th>ATC code</th>
</tr>
</thead>
<tbody>
<tr>
<td>fexofenadine</td>
<td>R06A X26</td>
</tr>
<tr>
<td>fluoride, combinations</td>
<td>A12C D51</td>
</tr>
<tr>
<td>gamolenic acid, combinations</td>
<td>D11A X52</td>
</tr>
<tr>
<td>hydroxocobalamin</td>
<td>V03A B33</td>
</tr>
<tr>
<td>imiquimod</td>
<td>D06B B10</td>
</tr>
<tr>
<td>lactobacillus fermentum</td>
<td>G01A X14</td>
</tr>
<tr>
<td>lysine</td>
<td>B05X B03</td>
</tr>
<tr>
<td>mepartricin</td>
<td>G04B X12</td>
</tr>
<tr>
<td>montelukast</td>
<td>R03D C03</td>
</tr>
<tr>
<td>orlistat</td>
<td>A08A B01</td>
</tr>
<tr>
<td>nelfinavir</td>
<td>J05A E04</td>
</tr>
<tr>
<td>phospholipids, microspheres of</td>
<td>V08D A01</td>
</tr>
<tr>
<td>proguanil, combinations</td>
<td>P01B B51</td>
</tr>
<tr>
<td>propentofylline</td>
<td>N06B C02</td>
</tr>
<tr>
<td>rimexolone</td>
<td>S01B A13</td>
</tr>
<tr>
<td>saruplase</td>
<td>B01A D08</td>
</tr>
<tr>
<td>technetium([^m]Tc)(votumumab</td>
<td>V09I A04</td>
</tr>
<tr>
<td>temozolomide</td>
<td>L01A X03</td>
</tr>
<tr>
<td>zolmitriptan</td>
<td>N02C C03</td>
</tr>
</tbody>
</table>

### Change of name:
**previous:**
air-filled microspheres of human albumin

**new:**
albumin, human, microspheres of

### New DDDs:

<table>
<thead>
<tr>
<th>INN/common name</th>
<th>DDD</th>
<th>Unit</th>
<th>Route of administration</th>
<th>ATC code</th>
</tr>
</thead>
<tbody>
<tr>
<td>dirithromycin</td>
<td>0.5</td>
<td>g</td>
<td>O</td>
<td>J01F A13</td>
</tr>
<tr>
<td>fexofenadine</td>
<td>120</td>
<td>mg</td>
<td>O</td>
<td>R06A X26</td>
</tr>
<tr>
<td>ibutilide</td>
<td>2.5</td>
<td>mg</td>
<td>O</td>
<td>L02B G04</td>
</tr>
<tr>
<td>letrozole</td>
<td>0.3</td>
<td>g</td>
<td>O</td>
<td>A10B F02</td>
</tr>
<tr>
<td>miglitol</td>
<td>60</td>
<td>mg</td>
<td>Inhal</td>
<td>N07B A01</td>
</tr>
<tr>
<td>nicotine</td>
<td>10</td>
<td>mg</td>
<td>O</td>
<td>N05A H03</td>
</tr>
<tr>
<td>olanzapine</td>
<td>6</td>
<td>mg</td>
<td>O</td>
<td>N04B C04</td>
</tr>
<tr>
<td>ropinirole</td>
<td>16</td>
<td>mg</td>
<td>O</td>
<td>N05A E03</td>
</tr>
<tr>
<td>sertraline</td>
<td>10</td>
<td>mg</td>
<td>O</td>
<td>N02C C01</td>
</tr>
<tr>
<td>valsartan</td>
<td>80</td>
<td>mg</td>
<td>O</td>
<td>C09C A03</td>
</tr>
<tr>
<td>* diclofenac combinations (correspond to the DDD for diclofenac)</td>
<td>0.1</td>
<td>g</td>
<td>O,P,R</td>
<td>M01A B55</td>
</tr>
</tbody>
</table>

* *additional information*
Recent Publications and Documents

Drugs for the elderly

Many elderly people often have concomitant illnesses and this can lead to the prescription of several different medicines at the same time. While many of these drugs help improve the survival and quality of life of elderly people, it is estimated that as many as one-fifth of patients entering a geriatric ward of a general hospital have symptoms attributable to effects from prescribed drugs.

The aim of Drugs for the elderly is to promote drug use that is efficacious and safe. Presented in the form of a pocket-size book, it is a convenient guide to possible side-effects of those drugs most often used in treating the elderly. For doctors, it constitutes a source of essential facts for safe prescribing. For pharmacists and nurses, it provides a guide on what the patient needs to know, and is a quick reference to the many differences in the treatment of young and old. It also points to alternative treatments which are equally effective or safer.

The most effective way to ensure the appropriate use of prescription drugs is through the training of health personnel, and this book will be indispensable for medical, pharmacy and nursing schools around the world.


Rapid examination methods against counterfeit and substandard drugs

The provision of safe and effective pharmaceutical products of good quality is vitally important for health care services, for use in the diagnosis, treatment or prevention of disease. Unfortunately, the expansion of international trade has led to the infiltration of counterfeit and substandard drugs into many markets.

This manual describes rapid analytical methods for the detection of counterfeit and substandard drugs. It also gives easy-to-follow directions on how to identify abnormalities in external packaging, outer appearance and contents of fake products, and how to inspect for tampering. These rapid examination methods are also complemented by instructions on the application of organoleptic inspection and thin layer chromatography. It is emphasized that any enforcement action involving counterfeit or substandard products should only be undertaken after a complete official laboratory analysis in accordance with national legal provisions in vigour.

Rapid examination methods against counterfeit and substandard drugs. Available from the Japan International Corporation of Welfare Services (JICWELS), Shinjuku Takasago Bldg. 10F, 16-5 Tomihisa-cho Shinjuku-ku, Tokyo 162, Japan. Fax number: 03 3225 6590.

Countering counterfeiting

Counterfeiting is one of the fastest growing economic crimes worldwide. It threatens the developed and developing world alike, undermining trade relations, scaring off vital new investment and endangering public health and safety. Legitimate manufacturers who invest heavily in the research and development of a product can suffer devastating losses and this leads to discouragement of further research spending, and the consequent slowing of technological innovation.

Countering counterfeiting: a guide to protecting and enforcing intellectual property rights provides an overview of how owners of intellectual property rights may defend themselves against counterfeiting. It describes the nature, scale and impact of product counterfeiting and outlines strategies for its prevention. Where companies have become the victims of counterfeiters, information is given on potential action.

Countering counterfeiting: a guide to protecting and enforcing intellectual property rights. Available from the Counterfeiting Intelligence Bureau, International Chamber of Commerce, Maritime House, 1 Linton Road, Barking, Essex IG1 8HG, United Kingdom. Fax number: 44 14953 2902. e-mail: pub@iccwbo.org
Malaria: a manual for community health workers

Community health workers can help in many ways to treat malaria and prevent new cases. This manual concentrates on activities that are within the competence of such health workers and feasible and affordable at the community level. Information is provided on the disease and its transmission, and on treatment schedules for different age groups, including advice in the event of treatment failure.

The manual will be particularly useful in training courses, or as a support to health education in the community. Practical rules for organizing anti-malaria work and community action to reduce the incidence of malaria are set out in two annexes.

Guidelines for the management of drug-resistant tuberculosis

About one-third of the world’s population is infected by *Mycobacterium tuberculosis* and, in 1995, there were nine million new cases of tuberculosis with three million deaths.

Effective tuberculosis control can be implemented using inexpensive, simple and largely standardized techniques, coupled with the managerial skills to implement them on a large intervention scale. Since 1992, the WHO Global Tuberculosis Programme has developed a strategy which has been successful in meeting the challenge of large-scale tuberculosis control.

One major obstacle to the successful implementation of treatment campaigns is the existence of multidrug-resistant tuberculosis and the need to use second-line drugs. Once a country has decided that it has a clear need for these drugs, they should be provided by a specialized unit working in close connection with a laboratory able to carry out cultures and reliable susceptibility tests of *M. tuberculosis*. The present handbook gives clear advice on this important issue.

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International Nonproprietary Names for Pharmaceutical Substances (INN)

RECOMMENDED International Nonproprietary Names (Rec. INN): List 38

Notice is hereby given that, in accordance with paragraph 7 of the Procedure for the Selection of Recommended International Nonproprietary Names for Pharmaceutical Substances [Off. Rec. Wild Health Org., 1955, 60, 3 (Resolution EB15.R7); 1969, 173, 10 (Resolution EB43.R9)], the following names are selected as Recommended International Nonproprietary Names. The inclusion of a name in the lists of Recommended International Nonproprietary Names does not imply any recommendation of the use of the substance in medicine or pharmacy. Lists of Proposed (1–73) and Recommended (1–35) International Nonproprietary Names can be found in Cumulative List No. 9, 1996.

Dénominations communes internationales des Substances pharmaceutiques (DCI)

Dénominations communes internationales RECOMMENDÉES (DCI Rec): Liste 38

Il est notifié que, conformément aux dispositions du paragraphe 7 de la Procédure à suivre en vue du choix de Dénominations communes internationales recommandées pour les Substances pharmaceutiques [Actes off. Org. mond. Santé, 1955, 60, 3 (résolution EB15.R7); 1969, 173, 10 (résolution EB43.R9)] les dénominations ci-dessous sont mises à l'étude par l'Organisation mondiale de la Santé en tant que dénominations communes internationales proposées. L'inclusion d'une dénomination dans les listes de DCI proposées n'implique aucune recommandation en vue de l'utilisation de la substance correspondante en médecine ou en pharmacie.

On trouvera d'autres listes de Dénominations communes internationales proposées (1–73) et recommandées (1–35) dans la Liste récapitulative No. 9, 1996.

Denominaciones Comunes Internacionales para las Sustancias Farmacéuticas (DCI)

Denominaciones Comunes Internacionales RECOMENDADAS (DCI Rec.): Lista 38

De conformidad con lo que dispone el párrafo 7 del Procedimiento de Selección de Denominaciones Comunes Internacionales Recomendadas para las Sustancias Farmacéuticas [Act. Of. Mund. Salud, 1955, 60, 3 (Resolución EB15.R7); 1969, 173, 10 (Resolución EB43.R9)], se comunica por el presente anuncio que las denominaciones que a continuación se expresan han sido seleccionadas como Denominaciones Comunes Internacionales Recomendadas. La inclusión de una denominación en las listas de las Denominaciones Comunes Recomendadas no supone recomendación alguna en favor del empleo de la sustancia respectiva en medicina o en farmacia.

Las listas de Denominaciones Comunes Internacionales Propuestas (1–73) y Recomendadas (1–35) se encuentran reunidas en Cumulative List No. 9, 1996.
**MODIFICATION**

This is to inform you that WHO will henceforth publish lists of recommended INNs **twice a year**.

This new measure is intended to provide information as soon as possible on the names that have reached the status of recommended INNs.

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**MODIFICATION**

L'OMS publiera désormais les listes des DCI recommandées **deux fois par an**.

Cette nouvelle mesure est destinée à informer les lecteurs dès que possible au sujet des dénominations ayant atteint le statut de DCI recommandée.

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**MODIFICACION**

De ahora en adelante, la OMS publicará **dos veces por año** las listas de DCI recomendadas.

Con esta nueva medida se quiere facilitar lo antes posible la información sobre las denominaciones a las que se ha asignado la condición de DCI recomendadas.
Latin, English, French, Spanish: Recommended INN

Chemical name or description; Molecular formula; Graphic formula

DCI Recommandée
Nom chimique ou description; Formule brute; Formule développée

DCI Recomendada
Nombre químico o descripción; Fórmula empírica; Fórmula desarrollada

abacavirum

abacavir
\( (1S,4R)-4-[2\text{-amino-6-(cyclopropylamino)-9H-purin-9-yl}]\text{-2-cyclopentene-1-methanol} \)

abacavir
\( ([1S,4R]-4-[2\text{-amino-6-(cyclopropylamino)-9H-purin-9-yl}]\text{cyclopent-2-ényl}]méthanol \)

abacavir
\( (1S,4R)-4-[2\text{-amino-6-(ciclopropilamino)-9H-purin-9-il}]\text{-2-ciclopenteno-1-metanol} \)

\( \text{C}_{14}\text{H}_{16}\text{N}_{6}\text{O} \)

aimotriptanum

aimotriptan
\( 1\text{-[\[3\text{-[2-(dimethylamino)ethyl]}\text{indol-5-yl}]methyl]sulfonyl]pyrrolidine} \)

aimotriptan
\( 1\text{-[\[3\text{-[2-(diméthylamino)éthyl]-1H-indol-5-yl}]méthyl]sulfonyl]pyrrolidine} \)

aimotriptán
\( 1\text{-[\[3\text{-[2-(dimetilamino)etil]}\text{indol-5-il}]metil]sulfonil]pirrolidina} \)

\( \text{C}_{17}\text{H}_{25}\text{N}_{3}\text{O}_{2}\text{S} \)
amlintidum

amlintide

L-lysyl-L-cysteinyl-L-asparaginyl-L-threonyl-L-alanyl-L-threonyl-L-cysteinyl-
L-alanyl-L-threonyl-L-glutaminyl-L-arginyll-L-leucyl-L-alanyl-L-asparaginyl-
L-phenylalaninyl-L-leucyl-L-valyl-L-histidyl-L-seryl-L-seryl-L-asparaginyl-
L-asparaginyl-L-phenylalaninylglycyl-L-alanyl-L-isoleucyl-L-seryl-L-seryl-
L-threonyl-L-asparaginyl-L-valyl-L-glucyl-L-seryl-L-asparaginyl-L-threonyl-
L-tyrosinamidcyclic(2→7)-disulfide

amlintide

(2→7)-disulfure cyclique de L-lysyl-L-cystéinyl-L-asparaginyl-L-thréonyl-L-alaniny-
L-thréonyl-L-cystéinyl-L-alanyll-L-thréonyll-L-thréonyll-L-alaniny-L-glutaminyl-
L-arginyll-L-leucyl-L-alanyl-L-asparaginyl-L-phenylalaninyl-L-leucyl-L-valyl-
L-histidylL-sériyl-L-sériyl-L-asparaginyl-
(2→7)-disulfuro cíclico de L-lisil-L-cisteinil-L-asparaginil-L-treonilL-alanil-
L-treonil-L-cisteinil-L-alanil-L-treonil-L-glutaminil-L-arginil-L-leucil-L-alanil-
L-asparaginil-L-phenilalanil-L-leucil-L-valli-L-histidil-L-seril-L-seril-L-asparaginil-
L-asparaginil-L-feniletanoligcil-L-alanil-L-isoleucil-L-leucil-L-seril-L-seril-
L-treonil-L-asparaginil-L-valiligcil-L-seril-L-asparaginil-L-treonil-
L-tyrosinamid

amlintida

(2→7)-disulfuro cíclico de L-lisil-L-cisteinil-L-asparaginil-L-treonilL-alanil-
L-treonil-L-cisteinil-L-alanil-L-treonil-L-glutaminil-L-arginil-L-leucil-L-alanil-
L-asparaginil-L-phenilalanil-L-leucil-L-valli-L-histidil-L-seril-L-seril-L-asparaginil-
L-asparaginil-L-feniletanoligcil-L-alanil-L-isoleucil-L-leucil-L-seril-L-seril-
L-treonil-L-asparaginil-L-valiligcil-L-seril-L-asparaginil-L-treonil-
C_{165}H_{261}N_{51}O_{55}S_{2}

avitriptanum

avitriptan

3-[3-[4-(5-methoxy-4-pyrimidinyl)-1-piperazinyl]propyl]-N-methylindole-
5-methanesulfonamide

avitriptan

[3-[3-[4-(5-méthoxypyrimidin-4-yl)pipérazin-1-yl]propyl]-1H-indol-5-yl]-
N-méthylméthanesulfonamide

avitriptán

3-[3-[4-(5-metoxi-4-pirimidinil)-1-piperazinil]propil]-N-metilindol-
5-metanosulfonamida

\[
\text{C}_{22}\text{H}_{30}\text{N}_{6}\text{O}_{3}\text{S}
\]
**bamaquimastum**

*bamaquimast*

3-(3-hydroxypropyl)-1-propyl-2(1H)-quinoxalinone methylcarbamate (ester)

*bamaquimast*

méthylcarbamate de 3-(3-oxo-4-propyl-3,4-dihydroquinoxalin-2-yl)propyle

*bamaquimast*

meticarbabamatoéster de 3-(3-hidroxipropl)-1-propil-2(1H)-quinoxalinona

\[C_{16}H_{21}N_3O_3\]

---

**basiliximabum**

*basiliximab*

immunoglobulin G 1 (human-mouse monoclonal CHI621 heavy chain anti-human interleukin 2 receptor), disulfide with human-mouse monoclonal CHI621 light chain, dimer

*basiliximab*

immunoglobuline G 1 (chaîne lourde de l'anticorps monoclonal chimérique homme-souris CHI621 dirigé contre le récepteur humain de l'interleukine 2), dimère du disulfure avec la chaîne légère de l'anticorps monoclonal chimérique homme-souris CHI621

*basiliximab*

inmunoglobulina G 1 (cadena pesada del anticuerpo monoclonal quimérico hombre-ratón CHI621 dirigido contra el receptor humano de la interleuquina 2), dimero del disulfuro con la cadena ligera del anticuerpo monoclonal quimérico hombre-ratón CHI621

---

**betadexum**

*betadex*

β-cyclodextrin

*betadex*

β-cyclodextrine

*betadex*

β-ciclodextrina

\[C_{42}H_{70}O_{35}\]
bimoclomol

\((\pm)-N-(2\text{-hydroxy-3-piperidinopropoxy})\text{nicotinimidylyl chloride}\)

chlorure de \(N-(2\text{RS}-2\text{-hydroxy-3-(piperidin-1-yl)propoxy})\text{pyridin-3-carboximidoyl}\)

cloruro de \((\pm)-N-(2\text{-hidroxi-3-piperidinopropoxi})\text{nicotinimidoyl}\)

\(C_{14}H_{20}ClIN_3O_2\)

[Diagram of bimoclomol structure]

blonanserinum

\(2-\text{(4-ethyl-1-piperazinyl)-4-(p-fluorophenyl)-5,6,7,8,9,10-hexahydrocyclo}\)
\(\text{octa}[b]\text{pyridine}\)

2-\(\text{(4-éthylpipérazin-1-yl)-4-(4-fluorophényl)-5,6,7,8,9,10-hexahydrocyclo}\)
\(\text{octa}[b]\text{pyridine}\)

2-\(\text{(4-etil-1-piperazinil)-4-(p-fluorofenil)-5,6,7,8,9,10-hexahidrociclo}\)
\(\text{octa}[b]\text{piridina}\)

\(C_{23}H_{30}FN_3\)

[Diagram of blonanserin structure]

brasofensisnum

\(3\beta-(3,4\text{-dichlorophenyl}-1\alpha,5\alpha\text{-tropane-2\alpha-carboxaldehyde}}\)
\((E)-(O\text{-methylxime})\)

\((1R,2R,3S,5S)-3\{3,4\text{-dichlorophényl}\}-8\text{-méthyl-8-azabicyclo[3.2.1]}\text{octane-2-carbaldéhyde (E)}-O\text{-méthylxime}\)

\(3\beta\{3,4\text{-diclorofenil}-1\alpha,5\alpha\text{-tropano-2\alpha-carboxaldehido (E)}-(O\text{-metiloxima}\)

\(C_{16}H_{12}Cl_2N_2O\)

[Diagram of brasofensine structure]
**brinzolamidum**

*brinzolamide*

\( (R)-4-(\text{ethylamino})-3,4\text{-dihydro-2-(3-methoxypropyl)-2H-thieno[3,2-e]-1,2-thiazine-6-sulfonamide 1,1-dioxide} \)

\( C_{12}H_{21}N_{3}O_{5}S_{2} \)

**cevimelinum**

*cevimeline*

\( (\pm)-\text{cis-2-methylspiro}[1,3\text{-oxathiolane-5,3'-quinuclidine}] \)

\( C_{10}H_{17}N_{OS} \)

**cizolirtinnum**

*cizolirtine*

\( (\pm)-5-[\alpha-2-(\text{dimethylamino})\text{ethoxy}]\text{benzyl}\]-1-methylpyrazole

\( C_{16}H_{21}N_{5}O \)
**Recommender INN:** List 38

**WHO Drug Information, Vol. 11, No. 3, 1997**

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**Dalcotidinum**

Dalcotidine

1-ethyl-3-[3-[(α-piperidino-m-tolyl)oxy]propyl]urea

1-éthyl-3-[3-[(pipéridino-1-yl)méthylphénoxy]propyl]urée

Dalcotidina

1-etil-3-[3-[(α-piperidino-m-toll)oxi]propil]urea

C₁₈H₂₉N₃O₂

---

**Daniplestimum**

Daniplestim


Daniplestim


Daniplestim


C₁₆₆H₉₀₉N₁₆₁O₁₆₆S₅

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**Dexefaroxanum**

Dexefaroxan

(+)-(R)-2-(2-ethyl-2,3-dihydro-2-benzofuranyl)-2-imidazoline

Dexéfaroxan

(+)-2-(2R)-2-éthyl-2,3-dihydrobenzofuran-2-y1]-4,5-dihydro-1H-imidazole

Dexefaroxán

(+)-(R)-2-(2-etil-2,3-dihidro-2-benzofuranil)-2-imidazolina

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elacridarum
elacridar
$4'\text{-}[2-(3,4\text{-dihydro}-6,7\text{-dimethoxy}-2(1\text{-H})\text{-isoquinolyl})\text{ethyl}]-5\text{-methoxy-9-oxo-4-acridancarboxanilide}$

elacridar
$N\text{-}[4\text{-}[2-(6,7\text{-diméthoxy-3,4\text{-dihydroisooquinoléin}-2(1\text{-H})\text{-éthyl})\text{phényl}]}\text{-}5\text{-méthoxy-9-oxo-9,10\text{-dihydroacridine-4-carboxamide}}$

elacridar
$4'\text{-}[2-(3,4\text{-dihidro-6,7-dimetoxy-2(1H)-isoquinoliléin})\text{etil}]-5\text{-metoxi-9-oxo-4-acridancarboxanilida}$

$C_{34}H_{33}N_3O_5$

edacimibum
edacimibe
cyclic isopropylidene $[(3,5\text{-di-tert-butil-4-hydroxanilino})\text{hexil}=\text{(p-neopentilbenzyl)amino}]\text{méthylene}\text{malonate}$

edacimibe
$5\text{-}[[3,5\text{-bis(1,1\text{-diméthyléthyl})-4-hydroxyphényl}])\text{amino}][4\text{-}(2,2\text{-diméthylpropyl)benzyl}])\text{hexilamino}][\text{méthylène}]\text{-}2,2\text{-diméthyl-1,3-dioxane-4,6-dione}$

edacimiba
$[(3,5\text{-di-terc-butil-4-hidroxianilino})\text{hexil(p-neopentilbencil)amino}=\text{metileno}])\text{malonato cíclico de isopropilideno}$

$C_{39}H_{58}N_2O_5$
eperezolidum
eperezolid
épérézolide
eperezolida
N-[(S)-3-[3-fluoro-4-(4-glycoloyl-1-piperazinyl)phenyl]-2-oxo-5-oxazolidinyl]methylacetamide
N-[(5S)-3-[3-fluoro-4-{4-[2-hydroxyacétyl]pipérazin-1-yl}phényl]-2-oxooxazolidin-5-yl[méthyl]acétamide
N-[(S)-3-[3-fluoro-4-(4-glicoloil-1-piperazínil)fenil]-2-oxo-5-oxazolidinil]metilacetamida
C₁₈H₂₃FN₄O₅

esatenololum
esatenolol
ésaténolol
esatenolol
2-[(2S)-2-hydroxy-3-(isopropylamino)propoxy]phenylacetamide
2-[(2S)-2-hidroxi-3-(isopropilamino)propoxi]fenil]acetamida
C₁₄H₂₂N₂O₃

faralimomabum
faralimomab
faralimomab
faralimomab
immunoglobulin G 1 (mouse monoclonal 64G12 γ1-chain anti-human interferon receptor), disulfide with mouse monoclonal 64G12 light chain, dimer
immunoglobuline G 1 (chaîne γ1 de l'anticorps monoclonal de souris (64G12) dirigé contre le récepteur humain des interférons de type I), dimère du disulfure avec la chaîne légère de l'anticorps monoclonal de souris 64G12
inmunoglobulina G 1 (cadena γ1 del anticuerpo monoclonal de ratón (64G12) dirigido contra el receptor humano de los interferones de tipo I), dimero del disulfuro con la cadena ligera del anticuerpo monoclonal de ratón 64G12
**gacyclidinum**  
gacyclidine  
1-[cis-2-methyl-1-(2-thienyl)cyclohexyl]piperidine  
gacyclidine  
1-[(1RS,2SR)-2-méthyl-1-(thiophén-2-yl)cyclohexyl]pipéridine  
gaciclidina  
1-[cis-2-metil-1-(2-tienil)ciclohexil]pipendina  
C_{16}H_{25}NS

**ganaxolonum**  
ganaxolone  
3α-hydroxy-3-methyl-5α-pregnan-20-one  
ganaxolone  
3α-hydroxy-3-méthyl-5α-prégnan-20-one  
ganaxolona  
3α-hidroxi-3-metil-5α-pregn-20-ona  
C_{22}H_{36}O_{2}

**hemoglobinum crosfumarilum**  
hemoglobin crosfumaril  
hemoglobin A₀ (human α₂β₂ tetrameric subunit), α-chain 99,99'-diamide with fumaric acid  
hémoglobine crosfumaril  
99,99'-diamide de la chaîne α de l’hémoglobine A₀ (sous-unité tétramérique α₂β₂ humaine) avec l’acide fumarique  
hemoglobina crosfumarilo  
99,99'-diamida de la cadena α de la hemoglobina A₀ ( subunidad tetramérica α₂β₂ humana), con el ácido fumárico
**Recomended INN: List 38**

**Indisetronum**

*indisetron*

\[N\{(3,9-dimethyl-endo-3,9-diazabicyclo[3.3.1]non-7-yl)-1H-indazole-3-carboxamide\]*

**Indétron**

\[N\{(1R,5S,7S)-3,9-dimethyl-3,9-diazabicyclo[3.3.1]non-7-yl]-1H-indazole-3-carboxamide\]

**Indisetrón**

\[N\{(3,9-dimetil-endo-3,9-diazabicielo[3.3.1]non-7-yl)-1H-indazol-3-carboxamida\]

\[C_{17}H_{23}N_{5}O\]

![Chemical Structure of Indisetronum](attachment:indisetronum.png)

**Insulinum aspartum**

*insulin aspart*

\[28^B-L-aspartic acid-insulin (human)\]

*insuline asparte*

\[28^B-acide L-aspartique]insuline humaine\]

*insulina asparta*

\[28^B-L-acido aspártico-insulina(humana)\]

\[C_{256}H_{381}N_{65}O_{78}S_{6}\]

![Chemical Structure of Insulinum Aspartum](attachment:insulinum_aspartum.png)

**Insulinum glarginum**

*insulin glargine*

\[21^A-glycine-30^Aa-L-arginine-30^Ab-L-arginineinsulin (human)\]

*insuline glargine*

\[21^A-glycine]30^Aa-L-arginine-30^Ab-L-arginine-insuline humaine\]

*insulina glargina*

\[21^A-glicina-30^Aa-L-arginina-30^Ab-L-argininainsulina (humana)\]

\[C_{267}H_{404}N_{72}O_{78}S_{6}\]

![Chemical Structure of Insulinum Glarginum](attachment:insulinum_glarginum.png)
iometopane (\(^{123}\))
iometopane (\(^{123}\))
iométopane (\(^{123}\))
iometopano (\(^{123}\))

\[
\text{methyl } 3\beta-(p^{123}\text{iodo} \text{phenyl})-1\alpha,5\alpha\text{-tropane-2}\beta\text{-carboxylate}
\]
\[(1R,2S,3S,5S)-3-(4-^{123}\text{iodo} \text{phényl})-8\text{-méthyl}-8\text{-azabicyclo[3.2.1]octane-2} \text{-carboxylate}
\]
\[
3\beta-(p^{123}\text{iodo} \text{fenil})-1\alpha,5\alpha\text{-tropano-2}\beta\text{-carboxilato}\text{ de métilo}
\]
\[
C_{16}H_{20}^{123}\text{INO}_2
\]

\[
\text{israpafantum}
\]
\[
\text{israpafant}
\]
\[
\text{israpafant}
\]
\[
\text{israpafant}
\]

\[
(\pm)-4-(o\text{-chlorophenyl})-2-(p\text{-isobutylphenethyl})-6,9\text{-dimethyl}-6\text{H-thieno}[3,2-f-s-triazolo}[4,3-a][1,4]\text{diazepine}
\]
\[(6RS)-4-(2\text{-chlorophényl})-6,9\text{-diméthyl-2-[2-[4-(2\text{-méthylpropyl})phényl]éthyl]}-6\text{H-thiéno}[3,2-f][1,2,4]\text{triazolo}[4,3-a][1,4]\text{diazépine}
\]
\[(\pm)-4-(o\text{-chlorofenil})-2-(p\text{-isobutilfenetil})-6,9\text{-dimétil-6Htieno}[3,2-f-s-triazolo}[4,3-a][1,4]\text{diazipina}
\]
\[
C_{28}H_{29}\text{ClN}_{4}\text{S}
\]

\[
\text{keliximabum}
\]
\[
\text{keliximab}
\]
\[
\text{kéliximab}
\]

\[
\text{immunoglobulin G 1 (human-Macaca monoclonal CE9.1 \gamma 1-chain anti-human antigen CD 4), disulfide with human-Macaca monoclonal CE9 1 \kappa-chain, dimer}
\]
\[
\text{immunoglobuline G 1 (chaîne \gamma 1 de l’antigène CD 4 humain), dimère du disulfure avec la chaîne \kappa de l’antigène mono}
\]
\[
\text{immunoglobulina G 1 (cadena \gamma 1 del antígeno CD4 humano), dimero del disulfuro con la cadena \kappa del antígeno mono}
\]
\[
\text{immunoglobulina G 1 (cadena \gamma 1 del antígeno CD4 humano), dimero del disulfuro con la cadena \kappa del antígeno monoclonal dimérico hombre-macaco CE9.1}
\]

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lanoteplasum

$N\{N^2-(N\text{-glycyl-L-alanlyl)}\text{-L-arginyln}]\text{-117-L-glutamine-245-L-methionine-}(1-5)-(87-527)\text{-plasminogen activator (human tissue-type protein moiety)}$

lanotéplase

$N\{N^2-(N\text{-glucyl-L-alanlyl}])\text{-L-arginyln}]\text{-117-L-glutamine-245-L-méthionine-}(1-5)-(87-527)\text{-activateur du plasminogène (type tissulaire humain, partie protéique)}$

lanoteplasa

$N\{N^2-(N\text{-glicyl-L-alanil})\text{-L-arginil}]\text{-117-L-glutamina-245-L-metionina-}(1-5)-(87-527)\text{-activador del plasminógeno (tipo tisular humano, fracción proteica)}$

$C_{219}H_{332}N_{63}O_{66}S_{29}$

lasinavirum

lasinavir

$\text{tert-butyl}\{\alpha\text{-S,3,3,3}}]-1\text{-hydroxy-3}]-\{[(1\text{-S,3R})]-1\text{-[2-methoxyethyl]carbamoil}]\text{-2-methylpropylo[carbamoil]}\text{-4-(2,3,4-trimethoxyphenyl)butyl[phenetyl]}\text{-carbamate}$

lasinavir

$[(1\text{-S,2,2,2,2})]-1\text{-benzyl-2-hydroxy-5}]-\{[(1\text{-S}]-1\text{-[2-méthoxyéthyl]carbamoil}]\text{-2-méthylpropylo[amino]}\text{-5-oxo-4-(2,3,4-triméthoxybenzyl)pentyl[carbamate de 1,1-diméthylethyle}$

lasinavir

$\{[(\alpha\text{-S})]-1\text{-hidroxi-3}]-\{[(1\text{-S}]-1\text{-[2-metoxietil]carbamoil]}\text{-2-metilpropylo[carbamoil]}\text{-4-(2,3,4-trimetoxifenil)butyl[feneti]}\text{[carbamato de tert-butil]}}$
**ledoxantronum**

**ledoxantrone**

$5\cdot[(2\cdot\text{aminoethyl})\cdot\text{amino}]\cdot2\cdot[2\cdot(\text{diethylamino})\cdot\text{ethyl}]\cdot2\cdot[H]_{1}\cdot\text{benzothiopyran}= [4,3,2-\text{cd}]\cdot\text{indazol-8-ol}$

**ledoxantrone**

$5\cdot[(2\cdot\text{aminoethyl})\cdot\text{amino}]\cdot2\cdot[2\cdot(\text{diethylamino})\cdot\text{ethyl}]\cdot2\cdot[H]_{1}\cdot\text{benzothiopyran}= [4,3,2-\text{cd}]\cdot\text{indazol-8-ol}$

**ledoxantrona**

$5\cdot[(2\cdot\text{aminoetil})\cdot\text{amino}]\cdot2\cdot[2\cdot(\text{dietilamino})\cdot\text{etil}]\cdot2\cdot[H]_{1}\cdot\text{benzothiopiran}= [4,3,2-\text{cd}]\cdot\text{indazol-8-ol}$

$C_{29}H_{30}N_{9}O_{9}$

**linezolidum**

**linezolid**

$N\cdot[[(S)\cdot3\cdot(3\cdot\text{fluoro-4\cdotmorpholinophenyl})\cdot2\cdot\text{oxo-5\cdotoxazolidiny}]\cdot\text{methyl}]\cdot\text{acetamide}$

**linézolid**

$N\cdot[[(S)\cdot3\cdot(3\cdot\text{fluoro-4\cdotmorpholin-4\cdotyl})\cdot\text{phenyl}]\cdot2\cdot\text{oxoxazolidin-5\cdotyl}]\cdot\text{methyl}]\cdot\text{acetamide}$

**linezolid**

$N\cdot[[(S)\cdot3\cdot(3\cdot\text{fluoro-4\cdotmorfolinofenil})\cdot2\cdot\text{oxo-5\cdotoxazolidinm}]\cdot\text{metil}]\cdot\text{acetamida}$

$C_{16}H_{20}FN_{3}O_{4}$
**Lintuzumab**


**Metesindum**

Metesind is 4-[[α-[[2-aminobenzoc[cd]indol-6-yl)methylamino]-p-toly]sulfonyl]morpholine.

**Milfasartanum**

Milfasartan is methyl 2-[[4-butyl-2-methyl-6-oxo-5-[p-(o-1H-tetrazol-5-ylphenyl)benzyl]-1(6H)-pyrimidinyl]methyl]-3-thiophencarboxylate.

C30H30N6O3S
minalrestatum
minalrestat
\((\pm)-2-(4\text{-bromo}-2\text{-fluorobenzyl})-6\text{-fluorospiro}\{\text{isoquinoline-4(1H)},3\text{-pyrrolidine}\}-1,2',3,5'(2H)-\text{tetrone}\)

C\(_{19}\)H\(_{11}\)BrF\(_2\)N\(_2\)O\(_4\)

nagrestipenum
nagrestipen
26-L-alaninelymphokine MIP 1\(\alpha\) (human clone pAT464 macrophage inflammatory)

nagrestipen
[26-L-alanine]lymphokine MIP 1\(\alpha\) (clone pAT464 de macrophage inflammatoire humain)

nagrestipen
[26-L-alanina]linfoquina MIP 1\(\alpha\) (clon pAT464 de macrófago inflamatorio humano)

C\(_{338}\)H\(_{516}\)N\(_{88}\)O\(_{108}\)S\(_4\)

nelfinavirum
nelfinavir
\((3S,4aS,8aS)-N\text{-tert-butyl}-2\{[2R,3R]-3\{3,2\text{-cresotamido}\}-2\text{-hydroxy-4-(phenylthio)butyl}\}\text{decahydro-3-isoquinolinecarboxamide}\)

nelfinavir
\((3S,4aS,8aS)-N\{1,1\text{-diméthyléthyl}\}-2\{[2R,3R]-2\text{-hydroxy-3\{-3\text{-hydroxy-2-méthylbenzoyl\}amino}\}-4\{\text{phénylsulfanyl\}butyl}\}\text{décahydrosquinoléine-3-carboxamide}\)

nelfinavir
\((3S,4aS,8aS)-N\text{-terc butil}-2\{[2R,3R]-3\{3,2\text{-cresotamido\}-2\text{-hidrox-4-fenilito\}butil}\text{decahidro-3-isoquinolinacarboxamida}\)
nerelimomabum
nerelimomab
immunoglobulin G 1 (mouse monoclonal BAYX1351 γ1-chain anti-human tumor necrosis factor α), disulfide with mouse monoclonal BAYX1351 light chain, dimer

nérélimomab
immunoglobuline G 1 (chaîne γ1 de l'anticorps monoclonal de souris BAYX1351 dirigé contre le facteur de nécrose tumorale α humain), dimère du disulfure avec la chaîne légère de l'anticorps monoclonal de souris BAYX1351

nerelimomab
immunoglobulina G 1 (cadena ligera mouse monoclonal BAYX1351 γ1-chain anti-human tumor necrosis factor α), disulfide with mouse monoclonal BAYX1351 light chain, dimer

omiloxetinum
omiloxetine
4'-fluoro-2-[trans-4-(p-fluorophenyl)-3-[3,4-(methyleneoxy)=phenoxy)methyl]piperidino]acetophenone

omiloxétine
2-[(3RS,4SR)-3-[(1,3-benzodioxol-5-yloxy)méthyl]-4-(4-fluorophényl)]=pipéridin-1-yl]-1-(4-fluorophényl)éthanone

omiloxetino
4'-fluoro-2-[trans-4-(p-fluorofenil)-3-[3,4-(metilenodiox)=fenoxi)méthyl]piperidino]acetofenona

C_{27}H_{29}F_{2}NO_{4} and enantiomer et l'énantiomère y enantiómero
Opratoni iodidum
Opratoni iodide
Iodure d’opratonium
Ioduro de opratonio

Trimethyl[3-(undecenamido)propyl]ammonium iodide
Iodure de N,N,N-triméthyl-3-(undéc-10-énylamino)propan-1-aminium
Ioduro de trimetil[3-(undecenamido)propil]ammonio

C₁₇H₃₅IₙN₂O

Oprelevekinum
Oprelevekin
Oprelékine
Oprelevkin

2-178-interleukin 11 (human clone pXM/IL-11)
2-178-interleukine 11 (clone humain pXM/IL-11)
2-178-interleuquina 11 (clon humano pXM/IL-11)

C₈₅₄H₁₄₁₁N₂₅₃O₂₃₅S₂

Osutidinum
Osutidine
Ousutidine
Ousutidina

(±)-N-[(E)-[(p,β-dihydroxyphenethyl)amino][2-[[5-[(methylamino)=methyl][furfuryl]thio]ethyl][amino][methylene]methanesulfonamide
(E)-1-[(2RS)-2-hydroxy-2-[4-hydroxyphényl]éthyl]-3-[[5-[[méthylamino]=métily]-2-furil][méthyl][sulfanyl]éthyl]-2-[(méthylsulfonyl]guanidine
(±)-N-[(E)-[(p,β-dihidroxifenetil)amino][2-[[5-[[metilamino]=metil][furfuril][tio]etil]amino][metilenio][metanosulfonamida

C₁₉H₂₈N₄O₆S₂

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pelubiprofenum
pelubiprofen
(±)-p-[(E)-2-oxocyclohexylidene]methyl]hydratropic acid

pé lubiprofène
acide (2RS)-2-[4-[(E)-2-oxocyclohexylidine]methyl]phényl]propanoïque

pelubiprofeno
ácido (±)-p-[(E)-2-oxociclohexilideno]metil]hidratrópico

\[ \text{C}_{16}\text{H}_{18}\text{O}_{3} \]

pelubiprofenum
pelubiprofen
(±)-p-[(E)-2-oxocyclohexylidene]methyl]hydratropic acid

pé lubiprofène
acide (2RS)-2-[4-[(E)-2-oxocyclohexylidine]methyl]phényl]propanoïque

pelubiprofeno
ácido (±)-p-[(E)-2-oxociclohexilideno]metil]hidratrópico

\[ \text{C}_{16}\text{H}_{18}\text{O}_{3} \]

and enantomer
et énantiomère
y enantiómero

pumaprazolum
pumaprazole
methyl 2-[[2,3-dimethylimidazo[1,2-a]pyridin-8-yl]amino]methyl]3-methylcarbanilate

pumaprazole
2-[[2,3-diméthylimidazo[1,2-a]pyridin-8-yl]amino]méthyl]3-méthylphényl]carbamate de méthyle

pumaprazol
2-[[2,3-dimetilimidazo[1,2-a]pirídin-8-il]amino]metil]-3-metilcarbanilato de metilo

\[ \text{C}_{19}\text{H}_{22}\text{N}_{4}\text{O}_{2} \]

pumaprazolum
pumaprazole
methyl 2-[[2,3-dimethylimidazo[1,2-a]pyridin-8-yl]amino]methyl]3-methylcarbanilate

pumaprazole
2-[[2,3-diméthylimidazo[1,2-a]pyridin-8-yl]amino]méthyl]3-méthylphényl]carbamate de méthyle

pumaprazol
2-[[2,3-dimetilimidazo[1,2-a]pirídin-8-il]amino]metil]-3-metilcarbanilato de metilo

\[ \text{C}_{19}\text{H}_{22}\text{N}_{4}\text{O}_{2} \]

quilostigminum
quilostigmine
(3aS,8aR)-1,2,3,3a,8,8a-hexahydro-1,3a,8-trimethylpyrrolo[2,3-b]indol-5-yl 3,4-dihydro-2(1H)-isoquinolincarboxylate

quilostigmine
3,4-dihydrosoquinolinen-2(1H)-carboxylate de (3aS,8aR)-1,3a,8-triméthyl-1,2,3,3a,8,8a-hexahydro[2,3-b]indol-5-yile

quilostigmina
3,4-dihidro-2(1H)-isoquinolinacarboxilato de (3aS,8aR)-1,2,3,3a,8,8a-hexahidro-1,3a,8-trimetilpirrolo[2,3-b]indol-5-ilo

\[ \text{C}_{20}\text{H}_{27}\text{N}_{3}\text{O}_{2} \]
**retigabinum**
retigabine
rétigabine
retigabina

ethyl 2-amino-4-[(p-fluorobenzyl)amino]carbanilate

![Chemical Structure](image)

**sabcomelinum**
sabcomeline
sabcoméline
sabcomelina

(R)-3-quinuclidineglyoxylonitrile (Z)-(O)-methylxime

![Chemical Structure](image)

**scopinastum**
scopinast
scopinast
escopinast

7-[3-[4-[bis(p-fluorophenyl)hydroxymethyl]piperidino]propoxy]-6-methoxycoumarin

![Chemical Structure](image)
soretolidum
soretolide  2,6-dimethyl-\textit{N}(5-methyl-3-isoxazolyl)benzamide
sorétolide  2,6-diméthyl-\textit{N}(5-méthylisoxazol-3-yl)benzamide
soretolida  2,6-dimetil-\textit{N}(5-metil-3-isoxazolil)benzamida
\[\text{C}_{13}\text{H}_{14}\text{N}_{2}\text{O}_{2}\]

\[
\begin{array}{c}
\text{CH}_3 \\
\text{O} \\
\text{N} \\
\text{\[\text{CH}_3\text{\[\text{C}\].}}
\end{array}
\]

tasonerminum
tasonermín  1-157-tumor necrosis factor alfa-1a (human)
tasonermine 1-157-facteur de nécrose tumorale humain alfa-1a
tasonermina  1-157-factor de necrosis tumoral alfa-1a (humano)
\[\text{C}_{778}\text{H}_{1225}\text{N}_{215}\text{O}_{231}\text{S}_{2}\]

\begin{align*}
\text{VRSSRTPSD} & \quad \text{KPVAHVVanP} \\
\text{VEIRDNQLVV} & \quad \text{PSEGLYLiYS} \\
\text{SRIAVSYQTK} & \quad \text{VNNLSAIKSP} \\
\text{GGVFQLEKGD} & \quad \text{RLSAEINRPD} \\
\text{YLDFAESQV} & \quad \text{YFGIAL}
\end{align*}

technetium (\textsuperscript{99m}Tc)nofetumomab merpentanum

technetium (\textsuperscript{99m}Tc) nofetumomab merpentan

\text{immunoglobulin G 2b (mouse monoclonal NR-LU-10 Fab fragment anti-human tumor), disulfide with mouse monoclonal NR-LU-10 \(\kappa\)-chain, [N,N'-(2-formylyethyl)ethylene]bis[2-mercaptoacetamidato](4-)]N,N',S,S'oxo=\[\text{\textsuperscript{99m}Tc}\text{technetate}(1-) conjugate}

\text{technétium (\textsuperscript{99m}Tc) nofétumomab merpentan}

\text{immunoglobuline G 2b (fragment Fab de l'anticorps monoclonal de souris NR-LU-10 dirigé contre une tumeur humaine), disulfure avec la chaîne \(\kappa\) de l'anticorps monoclonal de souris NR-LU-10 conjuguée avec l'oxo-[[N,N'-(1-(3-oxopropyl)éthane-1,2-diy]bis[2-sulfanylacétamidato](4-)]N,N',S,S'=}\text{\textsuperscript{99m}Tc}\text{technétate}(1-)}

\text{tecnecio (\textsuperscript{99m}Tc) nofetumomab merpentán}

\text{immunoglobulina G 2b (fragmento Fab del anticuerpo monoclonal de ratón NR-LU-10 dirigido contra un tumor humano), disulfúr con la cadena \(\kappa\) del anticuerpo monoclonal de ratón NR-LU-10 conjugado con el oxo-[[N,N'-(1-(3-oxopropil)etano-1,2-diy]bis[2-sulfanilacetamidato](4-)]N,N',S,S'=}\text{\textsuperscript{99m}Tc}\text{tecnéctato}(1-)
temiverinum
temiverine 4-(diethylamino)-1,1-dimethyl-2-butylnyl (±)-α-phenylcyclohexaneglycolate
témivérine (2RS)-2-cyclohexyl-2-hydroxy-2-phénylacétate de 4-(diéthylamino)-1,1-diméthylbut-2-ynyle
temiverina (±)-α-fenilciclohexanoglicolato de 4-(dietilamino)-1,1-dimetil-2-butilno

\[C_{24}H_{35}NO_{3}\]

and enantiomer et l'énantiomère y enantiómero

ticolubantum
ticolubant (E)-6-[[2,6-dichlorophényl]thio]methyl]3-(phenethyloxy)-2-pyridineacrylic acid
ticolubant acide (E)-3-[6-[[2,6-dichlorophényl]sulfonyl]méthyl]-3-(2-phényléthoxy)prop-2-énoique
ticolubant ácido (E)-6-[[2,6-diclorofenil]tio]metil]3-(fenetiloxy)-2-piridinacrilico

\[C_{23}H_{32}Cl_{2}NO_{3}S\]

valspodarum


\[C_{63}H_{111}N_{11}O_{12}\]
vedaclidinum
vedaclidine
védaclidine
vedaclidina
 vedaclidina  
(S)-3-[4-(butylthio)-1,2,5-thiadiazol-3-yl]quinuclidine
(3S)-3-[4-(butylsulfanyl)-1,2,5-thiadiazol-3-yl]-1-azabicyclo[2.2.2]octane
(S)-3-[4-(butylthio)-1,2,5-thiadiazol-3-yl]quinuclidina

\[C_{13}H_{21}N_3S_2\]
AMENDMENTS TO PREVIOUS LISTS

Recommended International Nonproprietary Names (Rec. INN): List 30

p. 13 saruplasum
saruplase replace the definition by the following:
prourokinase (enzyme-activating) (human clone pUK4/pUK18), non-glycosylated

Recommended International Nonproprietary Names (Rec. INN): List 33

p. 6 nasaruplasum
nasaruplase replace the definition by the following:
prourokinase (enzyme-activating) (human clone pA3/pD2/pF1 protein moiety), glycosylated

Recommended International Nonproprietary Names (Rec. INN): List 36
(Denominations communes internationales recommandées (DCI Rec.): Liste 36)
Denominaciones Comunes Internacionales recomendadas (DCI Rec.): Lista 36

p. 150 levormeloxifenum
levormeloxifene replace the chemical name by the following:
(-)-1-[2-{4-\{3,4\}-7-methoxy-2,2-dimethyl-3-phenyl-4-chromanyl\} phenoxy]= ethylipyrrolidine
levormeloxifeno sustituyase el nombre químico por lo siguiente:
(-)-1-[2-{4-\{3,4\}-7-metoxi-2,2-dimetil-3-fenil-4-cromanil\} fenoxi]= etilpirrolidina
MODIFICATIONS APPORTÉES AUX LISTES ANTÉRIEURES

Dénominations communes internationales recommendées (DCI Rec.): Liste 30
(Informations pharmaceutiques OMS, Vol. 4, No. 3, 1990)

p. 14 saruplasum
    saruplase  
    remplacer la description par:
    pro-urokinase (activateur d'enzyme) (fraction protéique issue du clone humain
    pUK4/pUK18), non-glycosylée

Dénominations communes internationales recommendées (DCI Rec.): Liste 33
(Informations pharmaceutiques OMS, Vol. 7, No. 3, 1993)

p. 6 nasaruplasum
    nasaruplase  
    remplacer la description par:
    pro-urokinase (activateur d'enzyme) (fraction protéique issue du clone humain
    pA3/pD2/pF1), glycosylée

Pour toutes modifications apportées aux Dénominations communes internationales recommendées (DCI Rec.): Listes 34-37 voir page 181, section AMENDMENTS TO PREVIOUS LISTS.

MODIFICACIONES A LAS LISTAS ANTERIORES

Denominaciones Comunes Internacionales Recomendadas (DCI Rec.): Lista 30
(Información Farmacéutica, OMS, Vol. 4, No. 3, 1990)

p. 13 saruplasum
    saruplase  
    sustitúyase la descripción por la siguiente:
    prouroquinasa (activador de enzima) (fracción proteica procedente del clon
    humano pUK4/pUK18), no glucosilada

Denominaciones Comunes Internacionales Recomendadas (DCI Rec.): Lista 33

p. 6 nasaruplasum
    nasaruplase  
    sustitúyase la descripción por la siguiente:
    prouroquinasa (activador de enzima) (fracción proteica procedente del clon
    humano pA3/pD2/pF1), glucosilada

Para cualquier modificación de las Denominaciones Comunes Internacionales Recomendadas (DCI Rec.): Listas 34-37 vease página 181, sección AMENDMENTS TO PREVIOUS LISTS.
Procedure and Guiding Principles / Procédure et Directives / Procedimientos y principios generales

The text of the Procedures for the Selection of Recommended International Nonproprietary Names for Pharmaceutical Substances and General Principles for Guidance in Devising International Nonproprietary Names for Pharmaceutical Substances will be reproduced in uneven numbers of proposed INN lists only.

Les textes de la Procédure à suivre en vue de choix de dénominations communes internationales recommandées pour les substances pharmaceutiques et des Directives générales pour la formation de dénominations communes internationales applicables aux substances pharmaceutiques seront publiés seulement dans les listes impaires des DCI proposées.

El texto de los Procedimientos de selección de denominaciones comunes internacionales recomendadas para las sustancias farmacéuticas y de los Principios generales de orientación para formar denominaciones comunes internacionales para sustancias farmacéuticas aparece solamente en los números impares de las listas de DCI propuestas.